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DIRECT VISION SURGERY OF ACQUIRED AORTIC AND MITRAL VALVULAR STENOSIS UNDER HYPOTHERMIA

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THE surgical approach to the stenotic aortic valve continues to be one of the foremost dilemmas of the cardiac surgeon.

As early as 1948 Brock was successful in attacking the pulmonary valve by passing a valvulotome blindly through the wall of the right ventricle. Such blind instrumentation of the aortic valve, however, had the great disadvantage of producing aortic insufficiency, a lesion well tolerated in the pulmonic valve but one with more serious consequences than stenosis in the aortic valve. Because of this necessity of strict anatomic separation of the commissures in aortic stenosis, Bailey in 1952 introduced his well-known dilator which is passed blindly through the wall of the left ventricle into the aortic valve. The mortality with this operation, however, was very high, chiefly from fibrillation associated with the ventriculotomy and technical difficulties encountered in controlling hemorrhage from the high pressure in the left ventricular cavity. A later development of the blind technique was the approach to the valve from above by attaching a pouch to the ascending aorta through which the operator's

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finger or a dilator could be passed. Although this approach was an improvement over the ventricular route, some calcific valves cannot be opened with a finger fracture nor will their orifices admit the Bailey dilator. It has been realized, as is true with all intracardiac lesions, that direct vision of the valve offers the most favorable conditions for corrective repair.

The direct approach is accomplished either by hypothermia or with a pump-oxygenator. In spite of the comparatively early successful open attack on the pulmonic valve by Swan, cardiac surgeons shied away from the open operation on the aortic valve. This was because of their fear that fatal embolism would occur if the ostia of the coronary arteries were exposed through a direct vision aortotomy. Swan[16] in 1955 demonstrated experimentally first, and then on a human, that air did not move into the coronary arteries when their ostia were exposed to the atmosphere. This opened the way to direct vision attack on the aortic valve. Swan[16] in 1955 and Lewis[12] shortly thereafter demonstrated that under hypothermia and inflow occlusion one could obtain a direct look at the aortic valve in a dry field for up to 6 minutes. Swan and his co-workers[17] have reported encouraging results with this approach in 11 cases of congenital aortic stenosis.

The pump-oxygenator was also used to approach the aortic valve as early as 1954 by Clowes,[6] but whereas in all other cardiac defects the pump-oxygenator has the obvious advantage of providing a longer period of time to work in, this was not the case with aortic lesions since by their position they precluded coronary perfusion during the open portion of the procedure. Time was limited even more with the pump-oxygenator because the heart tolerance to ischemia was less than under hypothermia.

The experiments of Blanco and associates[3] provided a method for cardiac nourishment during the opening aortotomy by retrograde coronary sinus perfusion. This technique has been successfully applied clinically by Lillehei and his co-workers.[9, 13, 14] It has the disadvantage, however, of being technically cumbersome and does not provide a dry field in the area of the aortic valve. If the reparative surgery can be performed in a period of 6 minutes or less, inflow occlusion under hypothermia has several advantages over an extracorporeal oxygenator combined with retrograde perfusion. It can be carried out without the small, yet definite, complications of extracorporeal oxygenation. No extra members of a team are necessary and, in addition, as mentioned before, retrograde perfusion of the coronary sinus precludes a dry field in the area of the aortic valve.

The good results obtained by several groups using the hypothermia and inflow occlusion approach in the repair of congenital aortic stenosis demonstrate that this lesion can be well handled in a few minutes' time whether valvular or subvalvular.

On the other hand the pathology encountered in acquired aortic stenosis is not nearly so favorable for surgical correction. Seeing a number of comparatively young adults with acquired aortic stenosis go into cardiac decompensation with an irreversible outcome activated our interest in this disease and its possible surgical correction.

PATHOLOGY

We reviewed the autopsy records of 75 patients who died from marked aortic stenosis proved by postmortem examination at Stanford University Hospitals and San Francisco Hospital. The cause of death in these cases was cardiac failure or they were excluded from our series. It was interesting that rheumatic fever could be incriminated either by history or microscopic findings in almost all of these cases. On the other hand, there were a number of cases where the valve cusps were the site of marked arteriosclerotic changes with relative stenosis but these were usually found in patients who died from hypertensive or arteriosclerotic heart disease or of other causes and thus were excluded from our series. In these cases the functional valve opening was always at least 1.3 cm. in diameter or 0.90 cm.^{2} as opposed to diameters of less than 6 mm. in most of the cases thought to have succumbed to rheumatic aortic lesions. This would tend to confirm the critical aortic area of 0.75 cm.^{2} as postulated by Gorlin.[8] The arteriosclerotic valve changes consist of hardening of the valve leaflets with little or none of the commissural fusion that is characteristic of rheumatic disease. The average age at death in this series of patients with severe rheumatic aortic stenosis was 49.6 years. Sex was 4:1 in favor of men. It should be noted that there were several patients with congenital bicuspid valves with calcification binding the commissures and producing, at times, as severe stenosis as seen in the rheumatic cases.

One can conclude that rather marked arteriosclerotic changes in the aortic valve may narrow the valve considerably but never cause the impedence to flow that is seen in rheumatic disease which results in premature left heart failure.

CONCOMITANT LESIONS

Bailey[1] has frequently made a plea for exploration of the mitral and tricuspid valves during operations for acquired aortic stenosis. He states that in 44 per cent of his cases mitral stenosis has been found concomitantly with severe aortic stenosis. He does not give a figure for the incidence of tricuspid stenosis in his series but states that he routinely explores this valve also. Mitchell and associates[15] found a 33.2 per cent incidence of significant mitral stenosis accompanying severe aortic stenosis and a 5 per cent incidence of trivalvular stenosis. A study of our cases proved by autopsy showed a 43 per cent incidence of concomitant significant mitral stenosis. We found less than 2 per cent of concomitant tricuspid stenosis. Because of these findings we have adopted a policy of exploring the mitral valve with a finger immediately after the direct vision repair of the aortic valve. This has not presented any technical problem and has been rewarding in over 50 per cent of our operative cases.

LEFT HEART CATHETERIZATION

For the past 2 years we have been employing direct percutaneous left ventricular puncture as described by Brock[5] in the assessment of aortic stenosis. The procedure as we practice it requires but a few minutes and is performed during the course of our standard right heart catheterization. We feel that it is

simpler and safer than other more widely employed techniques of left heart catheterization. The gradients we have found both before and after valvulotomy have correlated well with our clinical evaluation of the patient. All of our patients who have been severely incapacitated have had gradients across the aortic valve ranging from 50 to 100 mm. Hg. Those with gradients below 30 mm. Hg have not been operated upon. Gradients found by postoperative recatheterization in 2 patients undergoing double valvulotomy have correlated well with their clinical improvement and with the changes we thought we had effected in the valves at surgery. Therefore, we feel that left heart catheterization by direct anterior percutaneous puncture of the left ventricle is a very valuable tool in selecting patients for operation and in evaluating their postoperative improvement objectively.

TECHNIQUE OF DIRECT VISION OPERATION EMPLOYING INFLOW OCCLUSION UNDER HYPOTHERMIA

General body cooling is carried out with ice packing until a body temperature of 34.5° C. is reached. The ice is removed and the patient is placed on a dry operating table. The temperature drifts to about 32.5° C. during the operation.

After initially employing a bilateral transverse third intercostal incision we now prefer the midline sternum-splitting incision.[7, 11] It has several advantages. First, it gives a much more generous exposure to the ascending aorta and to the superior and inferior venae cavae. Second, it is much faster to perform and is less traumatic to the patient both during and after the operation. The operation is carried out after the technique described by Swan.[16] In addition to isolating the two venae cavae for inflow occlusion, we also put umbilical tapes around the hila of both lungs. We have found that by this maneuver less blood is lost during the operation and, by releasing these tapes first on completion of the valvular repair, the aortotomy can be flooded with blood. In one case it was impossible to encircle the hila safely because of marked adhesive pleuritis and the value of this procedure became apparent. As so well described by Swan,[17] the handling of the aortotomy can be nerve-racking and the only difficult part of the operation. Two tricks have been useful in this connection. The first is to have two different-sized Beck vessel clamps available. The smaller one is used initially while making the aortotomy before the institution of inflow occlusion. The larger one is then reserved for reclamping the aortotomy at the completion of the valvular repair. Prior to the use of these two different-sized clamps, on several occasions we had difficulty grasping the entire aortic defect in the reapplication of the clamp.

Second, it is helpful to partially or temporarily occlude the cavae during the initial application of the Beck clamp to the side of the aorta; otherwise it is difficult to partially occlude a portion of its wall and may result in a laceration of the aorta. We have also come to employ a somewhat smaller and more proximally placed aortotomy than we initially did. It need be only about the length of the combined diameter of 2 fingers for adequate direct vision of the valve and is much more simply controlled and closed. Following the side occlusion of the aorta and the placement of the aortotomy in the occluded portion, the operating team is readied for the period of inflow occlusion. The operating table is tipped slightly away from the operator and leveled so that the right coronary artery orifice is uppermost. As the tapes are pulled up on the two cavae the anesthetist begins to keep time, calling off every half-minute elapsed. Immediately following, the tapes about both pulmonary hila are tightened. Next, the arch of the aorta distal to the aortotomy is occluded by a clamp. The Beck clamp on the aorta is removed and with the blood trapped in the lungs, only the blood contained in the left ventricle is expelled through this wound, and from then on the operating field is dry. A finger is introduced and an attempt is made to fracture the stenosed valve. In early favorable cases this may suffice in the same manner as a mitral valvulotomy. The

finger fracture may be only partially successful or, in many valves, the commissural fusion is so sclerotic that fracture with the finger is impossible (Fig. 1). If so, the valve is visualized and a large curved clamp is introduced through the small central lumen. In those cases resistant to finger fracture, opening of such a clamp inserted through the valve will often break one of the commissures and with the clamp holding open this partially divided valve, another commissure is divided under direct vision with heavy scissors. It is helpful to have an assistant hold back the proximal edge of the aortotomy with an Allis clamp or a vein retractor for optimum vision of the valve (Fig. 2). In the advanced cases several or all of the cusps are almost completely replaced by calcium and attempts at the autopsy table to trim off the calcium have not resulted in any more mobility but, rather, have resulted in perforation of the cusp or disintegration of it as a structure. We feel that if cutting of the commissures is necessary, division of two commissures is all that should be done in order to avoid the production of aortic regurgitation. In these severe cases it is readily apparent that, even after the commissures have been divided and the operator's finger can be inserted into the ventricular chamber, these cusps are so stiff that they will not be moved by the ordinary force of the contraction of the left ventricle. These are cases in which nothing short of a new valve will be lifesaving regardless of the length of time the operator has to work in.

Fig. 1.—Typical tight sclerotic and calcific aortic valve in a 39-year-old woman who died of her disease without attempted surgery.

We have found that the time necessary for these maneuvers, including accurate division of the commissures with scissors, is not over 2 minutes. In the heavily calcified type of case all the operator can hope for is an enlargement of the aortic lumen beyond the critical stenosis size, without adding to any existing regurgitation.

Following completion of valvulotomy, the steps to reconstitute the circulation are as follows. First, the tapes around the hila are released followed by the superior cava tape. This fills the heart and the aortotomy. If tapes have been used to occlude the lungs it has not been necessary to fill the aortotomy with Ringer's solution. When the aortotomy is completely submerged with blood or fluid, the aortotomy is reclamped with the larger of the two Beck clamps. We originally used stay sutures about the aortotomy but have found that they get in the way and do not currently employ them. It is sometimes helpful to pick up the corners of the aortic incision with Allis clamps during the maneuver of reapplying the large Beck clamp. Immediately following this, the inferior caval tape is released and the distal aortic clamp removed. If there is any leakage from the aortotomy after the application of the clamp, the clamp should be reapplied but only by first reoccluding the caval tapes

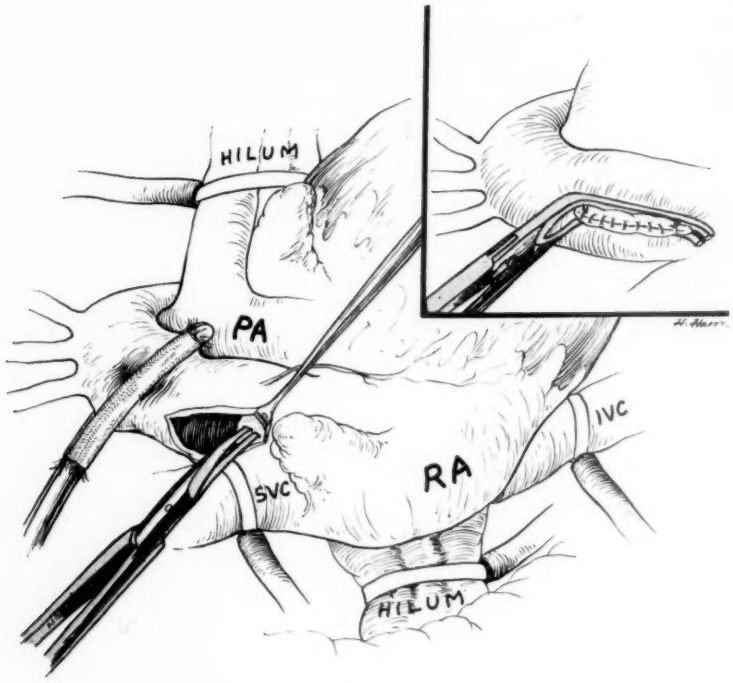


Fig. 2.—Diagram of heart and lungs with tapes about the cavae and hila, showing the site of aortotomy. Insert shows Beck clamp being used in the closure of the aorta.

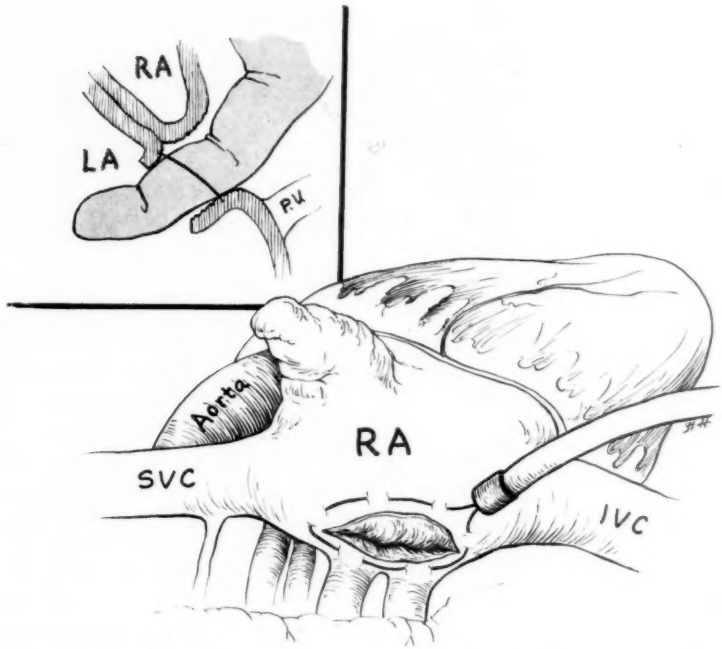


Fig. 3.—A view of the interatrial groove dissected from the right side showing the heavy purse string in place. Insert shows the finger inserted into the left atrium.

to decompress the aorta. Without this maneuver massive hemorrhage may occur or the aorta may be torn, both of which will likely result in an immediate fatality. The total period of inflow occlusion necessary is about 2½ minutes and occasionally 3 minutes for the entire operation. This is about the upper limit for inflow occlusion tolerance under normothermic conditions, and with the aid of hypothermia of about 32° C. an additional 4 or 5 minutes of safety is provided. It may well be that sometime in the future, as we acquire more experience, we will do these operations with inflow occlusion under normothermic conditions, avoiding any of the possible dangers of hypothermia.

Following our aortic valvulotomy a short period of rest is taken while the aortotomy wound is observed and the anesthetist areates the patient. If all is well we proceed to exploration of the mitral valve via the right-sided approach as described by Bailey.[1, 2] This is important because of the high incidence of concomitant significant mitral stenosis noted in our pathologic review of those patients who died with marked aortic stenosis. We have also found it difficult even after left and right heart catheterization to differentiate mitral stenosis from early failure of the left ventricle in these cases.

The technique is accomplished by having an assistant from the opposite side of the table gently retract the wall of the right atrium upward just below the insertion of the two venae cavae. At this level, a few millimeters above where the pulmonary veins enter the left atrium, there is some connective tissue and loose fat. By blunt dissection, this area of the interatrial septum is separated, clearing a portion of the top of the left atrium. A heavy nonabsorbable purse-string suture is placed in the left atrial wall here and is attached to a tourniquet which is held by the first assistant (Fig. 3). The central enclosed area is picked up with a forceps and a cut is made the size of the tip of the operator's index finger. The operator's index finger is immediately inserted into the left atrial chamber and, if there is any leakage about the finger, it is controlled by tightening the tourniquet. The exploration of the atrium and the technique of mitral valvulotomy is now carried out in the same fashion as in the well-known blind finger fracture from the left side. The only difference is that the valve is farther away from the operator from the right and considerably more reaching is required. Also, the posterior medial commissure is more easily split whereas the anterolateral one is less accessible. This technique of mitral valvotomy from the right side is accomplished more easily through a transverse chest incision than with the sternum splitting one but it can be done adequately through this approach. The aortic valvulotomy is the much more difficult part of the operation, so its infinitely easier approach through a sternum-splitting incision takes precedence. If the valve does not split easily, counter pressure is placed with the other hand over the left ventricle. After the fracture the purse-string suture is tied as the finger is removed from the left atrium. Usually no further suturing is required. If a tear of the atrium occurs or the purse string breaks, the hemorrhage can be controlled by approximating the walls of the atrium with a broad-based tissue forceps as described by Bailey.[2] We have not explored the tricuspid valve since our autopsy incidence of its concomitant stenosis is less than 2 per cent.

CASE REPORTS

CASE 1.—R. W. (SMH #5759W) was a 26-year-old white man with a history of rheumatic fever at age 5. The patient got along well except for severe dyspnea on exertion until 2 years prior to admission when he developed angina on exertion. There was no history of cardiac failure at any time.

Physical Examination.—Physical examination revealed a well-developed, well-nourished young man in no apparent distress. B. P. was 128/82. There was a palpable thrill over the base of the heart. There was a grade IV systolic murmur over the second right intercostal space transmitted into the neck. No other murmurs were heard. Chest films and ECG showed left ventricular hypertrophy. The clinical impression was pure aortic stenosis, marked. The patient was judged to be an excellent candidate for operation.

Operation.—The patient was operated upon July 22, 1957. Total body hypothermia of 32.0° C. was carried out and the chest opened. While dissecting the cavae and lung roots prior to placing tapes for occlusion, ventricular fibrillation occurred. At this time the heart rate was 48 and the body temperature 31.5° C. Cardiac massage was carried out and attempts to defibrillate the heart were unsuccessful. With inflow occlusion then of 5 minutes the aortic valve was exposed. It was calcific and had a lumen diameter of 2 mm. Two of the commissures were incised with heavy scissors under direct vision. Forty-five minutes after the fibrillation had begun, a regular cardiac rhythm was established. The patient's chest was closed and 3 hours later ventricular fibrillation again occurred which was not successfully reversed. Autopsy demonstrated a well-divided calcific aortic valve and no mitral stenosis. There was no evidence of myocardial infarction.

Comment.—In retrospect we feel that ventricular fibrillation occurred in this case from relative anoxia of the hypertrophied left ventricle. We did not have an indwelling arterial catheter to record the arterial pressure while under hypothermia. We now insist on this so that we can use vasopressors if the arterial pressure falls below 80. This was an extremely unfortunate outcome since the valvular stenosis was amenable to division.

CASE 2.—J. T. (SUH #358720), a 34-year-old white man, was admitted on March 5, 1957, with the chief complaint of shortness of breath of 2 years' duration. He gave a history of rheumatic fever at the age of 3 with frequent episodes of hot swollen joints until the age of 19. For 2 years prior to admission he had had progressive severe exertional dyspnea and probable angina. He had also had frequent episodes of pulmonary edema.

Physical Examination.—B. P. was 95/75; the pulse was irregular and weak. Point of maximum cardiac impulse was in the sixth intercostal space 2 cm. beyond the midclavicular line. There was a systolic thrill in the second right intercostal space. There was a grade III systolic murmur, loudest over the base of the heart and well heard into the neck, and a grade II systolic murmur at the apex transmitted to the left axilla. The clinical diagnosis was aortic and mitral stenosis. Right and left heart catheterization was carried out simultaneously to determine which valvular stenosis predominated and how severe they were as evidenced by gradients. The technique mentioned in this paper was employed.[1]

Preoperative right and left catheterization results: Aug. 20, 1957

RPA	40/24 mm. Hg
CO	2.8 L./min.
LV	163/7 mm. Hg
BA	102/65 mm. Hg
Aortic gradient	61 mm. Hg
Calculated aortic valve area	0.35 cm.^{2}

Conclusions.—Moderate elevation of the pulmonary artery pressure suggested some mitral stenosis. A gradient of 61 mm. Hg across the aortic valve indicated significant aortic stenosis. Therefore, operative attack on both valves was recommended.

Operation.—Operation was performed Aug. 22, 1957. With the patient under hypothermia and inflow occlusion of 2 minutes 45 seconds, the aortic valve was very satisfactorily opened by spreading scissors under direct vision. The lumen before fracture was estimated to be 3 mm. in diameter. Following this the mitral valve was split utilizing the blind right-sided approach to the left auricle. The patient's postoperative course was complicated by a staphylococcus bacteremia which responded to bacitracin.

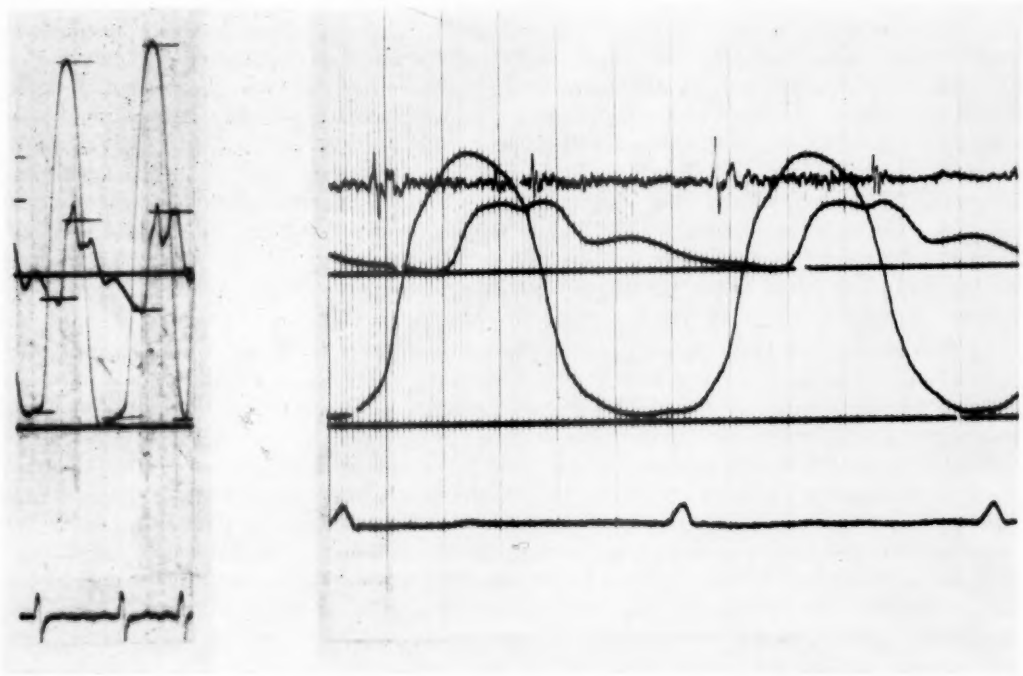
Postoperative right and left heart catheterization results:

RPA	32/18 mm. Hg
CO	4.1 L./min.
LV	126/5 mm. Hg
BA	104/71 mm. Hg
Aortic gradient	22 mm. Hg
Calculated aortic valve area	1.2 cm.^{2}

Course.—Eight months postoperative the patient's exercise tolerance is markedly increased. He can walk 6 blocks without stopping as compared to 100 yards before his valvulotomies. Fig. 4 shows the tracings of left ventricular and brachial artery pressures before and after valvulotomy. The aortic gradient is probably even further reduced in view of the fact that the flow across the valve is almost double that found on the first catheterization.

Comment.—This patient had an excellent result because the aortic valve was not heavily calcified and was easily fractured along the commissures.

CASE 3.—R. J. (SMH #7456W) was admitted Sept. 21, 1957. This 47-year-old white man's only childhood illness had been "pneumonia." He was first noted to have a heart murmur at the age of 25. Five years prior to admission he had the onset of squeezing substernal pain which had increased in frequency and intensity. In addition, he had had progressive shortness of breath for the past 3 years and, at the time of admission, he could walk only 100 yards without stopping.



A. *B.*

Fig. 4.—J. T. Simultaneous tracings from the left ventricle and the brachial artery before (*A*) and after (*B*) surgery to show the change in the gradient across the aortic valve.

Physical Examination.—Pulse was 76, small but regular. B. P. was 120/70. The patient was a well-developed, well-nourished, middle-aged man. Left apical impulse was visible lateral and below the nipple. There was a systolic thrill palpable over the right second intercostal space. At the base of the heart there was a grade IV systolic murmur which was transmitted into the neck. There were no diastolic murmurs. The electrocardiogram showed left ventricular hypertrophy. The chest film showed an enlarged left ventricle. The clinical impression was aortic stenosis, marked, etiology unknown. Left ventricular puncture was carried out on Sept. 18, 1957, and demonstrated a gradient of 110 across the aortic valve. Right heart catheterization was not performed. It was felt that this patient's life expectancy without surgery was very poor and thus aortic valvulotomy was recommended.

Operation.—On Sept. 23, 1957, aortic valvulotomy was carried out in the manner described under hypothermia and inflow occlusion. A moderately calcific valve with a lumen 3

mm. in diameter was found and was opened by incising two of the fused commissures with scissors. During the valvulotomy, the aortic incision was torn laterally and required additional time to close necessitating a period of inflow occlusion of 8 minutes 20 seconds. During this time fibrillation occurred which was successfully corrected.

Comment.—The patient has not had any angina since the operation, is much less dyspneic, and has returned to work. His good result again can be attributed to the finding of an aortic valve that was not too heavily calcified and was amenable to commissural division. Our present precautions with the aortotomy incision should prevent any future tears necessitating prolonged inflow occlusion.

CASE 4.—F. B. (SUH #E141350), a 41-year-old white woman was noted to have a heart murmur at the age of 25. Her only previous illness was "spinal meningitis" at age 14. At age 29 following pregnancy, she went into congestive failure. For the next 5 years prior to this admission she had been in congestive failure almost constantly. Fibrillation was noted for the first time one year prior to admission. For 2 years prior to admission she had had ascites. She had been bedridden for 18 months prior to this admission.

Physical Examination.—B. P. was 105/85, pulse 88, irregular, and small. The patient could not lie flat. There was distention of the neck veins, 2 plus ankle edema, and ascites. The heart was enlarged to percussion and there were murmurs of aortic and mitral stenosis. There was also a question of tricuspid insufficiency. A chest film demonstrated a grossly enlarged heart in both ventricular chambers and some fluid in the right chest. The cardiologists' opinion was grade IV rheumatic heart disease with severe aortic stenosis and probable mitral stenosis and tricuspid insufficiency. After an intensive course of medical treatment she continued to go downhill and it was felt that the only chance for survival would be to perform an aortic valvulotomy in spite of the almost prohibitive risk. Our usual work-up of right and left heart catheterization was omitted in this patient because of her severe condition.

Operation.—On Aug. 29, 1957, the operation was carried out under hypothermia with a total of 2½ minutes of inflow occlusion. The lung roots were not occluded in this case because of marked pleural adhesions and the precarious condition of the patient. When the aortotomy clamp was removed there was a large loss of blood which was contained in the dilated heart. The aortic valve was fractured by the operator's finger but the left ventricle never took over the load and failed upon reinstitution of the circulation. During cardiac massage a mitral valvulotomy was performed with ease on a fairly tight stenosis. All efforts to restart the heart were unsuccessful. Autopsy disclosed a heavily calcific aortic valve. Both the aortic and mitral orifices had been well opened, although the calcified aortic leaflets had poor mobility. The left ventricular wall was 2 cm. thick and showed patches of old scar indicating ischemic areas.

Comment.—We knew the risk here was almost prohibitive but a heroic attempt seemed warranted as the patient was obviously dying of a mechanical block. The large amount of blood lost may have been a factor in the failure of her heart to take over and has prompted us to make every effort now to trap part of this blood in the lungs by hilar tapes. Also we did not monitor her arterial pressure and it may have fallen below 80 before the valvulotomy causing ischemia to the thickened left ventricle and fibrillation.

CASE 5.—H. G. (SUH #264456), a 32-year-old woman, was admitted to the hospital on Feb. 15, 1958, with a history of St. Vitus' dance at the age of 11. She was noted at the age of 21 to have a heart murmur but was asymptomatic until the age of 28 when she had a sudden right-sided weakness and aphasia. For 2 years prior to her present admission she had had increasing episodes of angina, exertional dyspnea, and paroxysmal nocturnal dyspnea. There was no history of fibrillation, syncope, or failure. She was quite dyspneic with ordinary household activity. She could walk only 100 yards without stopping.

Physical Examination.—There was a prominent impulse in the fifth intercostal space midway between the nipple and axilla. There was a heave along the left sternal border. There was a harsh grade III-IV aortic pansystolic ejection murmur at the base transmitted into the neck. There was a grade II apical presystolic rumble in the fifth intercostal space

5 to 6 cm. left of the midline. There was a blowing diastolic murmur along the left sternal border and at the apex. The clinical diagnosis was aortic and mitral stenosis. Right and left heart catheterization was carried out simultaneously to determine which valvular stenosis predominated and how severe they were as evidenced by the gradients.

Results of right and left cardiac catheterization:

Feb. 20, 1958

RPA	53/21 mm. Hg
PA (wedge)	27 (mean) mm. Hg
BA	94/48 mm. Hg
LV	192/17 mm. Hg
Aortic gradient	98 mm. Hg

Conclusion.—Marked aortic and mitral stenosis was evident. Therefore, operative attack on both valves was recommended.

Operation.—On Feb. 28, 1958, with the patient under hypothermia and inflow occlusion of 2 minutes 30 seconds, the aortic valve was opened under direct vision. The aortic valve was very stenotic with a central opening estimated to be 6 mm. in diameter. The valve was very calcific and could not be fractured by the finger and required division with heavy scissors. After two commissures had been divided, the entire finger could be placed into the left ventricle. However, although we increased the aortic valve lumen, a very diseased poorly functioning valve remained. Next the mitral valve was opened blindly with the finger introduced into the left atrium from the right side. It was also very calcific and although the proximal phalanx of the operator's finger could be passed into the left ventricle at the completion of the valvulotomy, the valve still was not widely patent. The patient's postoperative course was uneventful.

Postoperative right and left heart catheterization results:

RPA	51/24 mm. Hg
PA (wedge)	23 (mean) mm. Hg
LV	195/9 mm. Hg
BA	133/69 mm. Hg
Aortic gradient	62 mm. Hg

Course.—Prior to operation she could not climb a flight of stairs or walk half a block on the level. Now 4 months after her operation she can climb stairs, walks 4 or 5 blocks before tiring, and feels like doing her own housework. There is a 36 mm. drop in the aortic gradient by recatheterization and this change may be greater because the increased flow across the valve minimizes the gradient change as the pressure gradient varies as a square of the flow. Although this patient's aortic valve is in large part replaced by calcium, valvulotomy has reduced her aortic gradient and markedly improved her exercise tolerance.

Case 6.—J. R. (SUH #367750), a 38-year-old white man, entered Stanford University Hospitals on May 19, 1958, from the Veterans Administration Hospital with a diagnosis of aortic stenosis, marked. The patient had rheumatic fever in his youth. He was well until 4 years prior to admission when he developed shortness of breath, exertional dyspnea, ankle swelling, and angina. A diagnosis of cardiac decompensation secondary to aortic stenosis was made on entry to the hospital. During the next 4 years he was forced to stop work completely with progressive incapacitation. During this time he had multiple hospitalizations for congestive failure. On a recent admission to the San Francisco Veterans Administration Hospital, consideration of surgery was entertained and left and right heart catheterization by the technique described previously was performed.

PA	66/45 mm. Hg
PA (wedge)	35 mm. Hg
LV	180/10 mm. Hg
BA	100/50 mm. Hg
Aortic gradient	80 mm. Hg

There was evidence of severe aortic stenosis with a gradient of 80 mm. Hg across the valve and a gradient of 25 mm. Hg across the mitral valve in addition to pulmonary hypertension which also suggested mitral stenosis.

Physical Examination.—Physical examination revealed a thin, tired young man who could not lie flat comfortably. Significant findings were confined to the cardiovascular system. There was no ankle edema, ascites, or enlarged liver. B. P. was 100/75; weak, regular pulse. There was a basilar thrill and a left ventricular heave. There was a grade IV systolic ejection murmur over the base of the heart. There was a grade III presystolic murmur at the apex and a high pitched diastolic murmur along the left sternal border.

The impression was rheumatic heart disease with marked aortic and mitral stenosis and chronic heart failure. Operation was offered as a possible chance in a poor-risk patient.

Fig. 5.

Fig. 6.

Fig. 5.—J. R. Appearance of aortic valve before fracture. All three commissures are fused and the valve leaflets are heavily calcified.

Fig. 6.—J. R. Size of aortic valve opening following division of two fused commissures.

Operation.—On May 23, 1958, with the patient under hypothermia with inflow occlusion of 2½ minutes, the aortic valve was approached directly. The diameter of the valve was estimated to be 5 mm. (Fig. 5). It was heavily calcified and could not be opened with finger fracture and required scissor division of two of the commissures. Following this, the mitral valve was explored from the right-sided approach and a moderately tight stenosis was fractured with the operator's finger. The patient withstood the procedure well and was in good

condition until 36 hours following operation when he suddenly went into shock and died. During his postoperative course he demonstrated a much improved peripheral pulse. Postmortem examination disclosed a well-divided aortic (Fig. 6) and mitral valve and a fresh myocardial infarction of the ventricular septum.

DISCUSSION

Although our series is small and our salvage rate poor, we have developed some definite ideas concerning the selection and handling of future patients. Usually the diagnosis is not difficult to make, but an important oversight may be the presence of concomitant mitral involvement and whether or not there is early failure. In analyzing our cases of double valve stenosis, we note that they seem to produce a picture contrasting to that found with either valve alone. In the double valve patient the onset of congestive heart failure preceded or was concomitant with the appearance of angina, a finding distinct from that usually associated with aortic stenosis alone. Also, in the double stenoses, the electrocardiographic changes of left ventricular hypertrophy were never clearly developed and the common association of a broad P wave in Leads II and III was noted. The diastolic murmur of mitral stenosis was always difficult to elicit in spite of the presence of a loud M_1 and of a loud P_2 and other evidences of pulmonary hypertension. In only one patient was the mitral opening snap easily detected. In another it was heard by less than half the examiners, and in the remaining 2 patients it was never heard. As stated earlier, we believe that percutaneous left ventricular puncture is useful in assessing the severity of aortic stenosis. However, the aortic gradient may be surprisingly low in the presence of a concomitant stenosis of the mitral valve.[18] Such a case is reported by Gorlin[8] in which there was only a 30 mm. Hg gradient recorded across the aortic valve in spite of an aortic valve area of only 0.4 cm.^{2}

The explanation here is that in the presence of mitral stenosis the stroke output is so low that only a relatively small gradient need be maintained across the aortic valve. If the stenotic mitral valve is opened in such a case without opening the aortic valve, the flow into the left ventricle is increased and, in turn, the gradient across the aortic valve rises. We routinely perform the aortic valvulotomy first in double valve stenoses to avoid exaggerating the aortic stenosis by first opening the mitral valve. Patients who have the signs and symptoms of significant aortic stenosis with a small measured gradient should be suspected of having concomitant mitral stenosis also. This is important in comparing gradients measured after operation, because either the correction of mitral or aortic obstruction or both will change the output and the gradient as it relates to the square of the flow across the valve. The optimal candidate for operation is 40 years old or under and probably no patient over 60 should be subjected to aortic valvulotomy. The magnitude of calcification of the aortic valve and the chances of improving its function rise rapidly after 35. Patients in severe cardiac decompensation, with perhaps the exception of those under 35 years of age, should not be operated upon. We feel that the recommendations of Wood[18] concerning the gradients across the aortic valve are a good guide to selection of patients; namely, choose those patients who have a gradient of 50 mm. Hg or better in pure stenosis and 25 mm. Hg or above when there is associated mitral stenosis.

In the development of mitral valve surgery, cardiologists and cardiac surgeons avoided the patients who were in failure, and, by operating upon the better risk patients, valvulotomy for mitral stenosis has been firmly established. Because of the dangerous technical difficulties encountered in the approach to the aortic valve, as mentioned earlier, aortic valvulotomy in acquired disease has fallen into disrepute and only those patients in chronic heart failure are referred for surgery. All but one of our patients have been in this category and thus the salvage rate is poor. However, we believe the technique employed is sound and safe and, if applied to better-risk patients, will establish a place for aortic valvulotomy along with other types of intracardiac surgery.

A final note about technique should be emphasized, namely, that the arterial pressure must be constantly monitored by an indwelling catheter during any cardiac operation done under inflow occlusion and hypothermia. This is particularly true when dealing with the thickened ischemic left ventricle found in acquired aortic stenosis. A fall in systemic pressure below 80 mm. Hg which can be unrecognized under hypothermia may lead to fatal, irreversible ventricular fibrillation. With monitoring of the pressure, any hypotension can be constantly corrected with a vasopressor drug with maintenance of adequate coronary flow.

Our present methods of aortic valvulotomy can be expected to give good and lasting results only in patients operated upon comparatively early in the course of their disease. The hope and expectation for the future are for a prosthetic valve or flap that can be satisfactorily attached in the root of the aorta to replace those valves found to be heavily calcified and immobile.

SUMMARY

1. The evolution of the development of surgery for the stenotic aortic valve is recounted and a plea for the direct vision approach made.

2. The advantages and disadvantages of the pump-oxygenator versus inflow occlusion under hypothermia are presented. Swan has demonstrated that inflow occlusion under hypothermia provides a very satisfactory approach to the correction of congenital aortic stenosis. However, the problem of acquired aortic stenosis is a dilemma because of the diseased nature of the valve.

3. We have reviewed the autopsy records of 75 patients who died from marked aortic stenosis. Cases were excluded unless their aortic orifice was below the critical size of 0.75 cm.^{2} These cases were all thought to be rheumatic in origin except for a few calcified bicuspid valves. In 43 per cent there was significant concomitant mitral stenosis.

4. The necessity of exploring the mitral valve at the same operation by the right-sided approach is stressed.

5. Direct anterior percutaneous left heart catheterization is used to evaluate the aortic gradient.

6. A comparatively low aortic gradient may be found in severe aortic stenosis that is accompanied by a significant concomitant mitral stenosis.

7. The case histories of 6 patients undergoing aortic and mitral valvulotomy under direct vision with hypothermia are presented. The lessons learned in each case are discussed.

8. We believe the technique outlined is sound and safe and, if applied to better-risk patients, will establish a place for aortic valvulotomy along with other types of intracardiac surgery.

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ADDENDUM

Since submitting this paper we have dropped the technique of encircling the pulmonary hila. We have found it unnecessary, time consuming, and difficult in many cases. By avoiding this point of the described technique we have also been able to avoid entering either pleural cavity on several occasions.

DISCUSSION

DR. ROBERT S. SHAW (Boston, Mass.).—As some of you know, we perfused about 40 stenotic aortic valves in the autopsy rooms before and after instrumenting them in an attempt to find out what happened in various techniques of valvulotomy to the degree of stenosis and the degree of regurgitation. I want to congratulate Dr. Connolly on his

work and his use of open aortotomy because I am sure he is right in that. There are a couple of things we might disagree with him on—on the basis of this autopsy experiment and on the basis of a few clinical cases.

First, our work showed that it is very definitely better, both from the point of view of stenosis and regurgitation, to divide all three commissures if it is indeed a tricuspid valve.

The other thing that we learned both in the autopsy room and also in the operating room is that it is rather dangerous, particularly on the very heavily calcified valves, to attempt to split them by dilatation, since one is very apt to split past the heavily calcified fusion of the cusps into the body of the leaflet with resulting regurgitation which may be inconsistent with life.

The other thing of interest is that after commissurotomy these valves move distressingly little during "systole" and "diastole" when viewed in a pulsatile perfusion apparatus. Surprisingly, the degree of stenosis remaining in these stiff valves is quite acceptably small and the competence of the valve is very good. I do not know how long these stiff, rather motionless valves will stay open after surgery. That is something we must find out.

DR. F. JOHN LEWIS (Chicago, Ill.).—Dr. Connolly and his associates have well described the accomplishments that are possible with this type of surgery and some of the problems that are encountered. I would merely like to add a few comments on some of the problems that have impressed us.

A common problem when you are able to see what you are doing is that it is easy to cut the valve and, therefore, you may do too much. Yet you may be faced with the problem of a valve that is already open in two of its commissures. I have heard a number of surgeons say that they are satisfied to open only two commissures and leave the third one fused. I have seen 2 or 3 cases now in which two commissures were widely open but the stenosis was due to heavy calcification. In effect you have a calcified disc with a very small hole in it.

This slide shows a postmortem study on a patient who died on the operating table. We made the small hole in a large one, achieving what we planned to do by cutting into the commissure. (Slide.) These are the pulse duplicator studies postmortem. The stenosis was completely relieved but we produced a complete insufficiency and because of that the patient did not survive the operation.

Now, in reviewing the few cases we have done, we find that the most successful ones are the ones that had only a small amount of calcium. This is reasonable. By careful preoperative x-ray studies including laminography you can probably separate cases with heavy calcium from those with only moderately heavy calcium, and I would be inclined to avoid trying to do any kind of an operation on those with heavy calcification, at least for the present.

There are many confusing aspects of the surgical treatment of this disease. Surgeons who now use the Brock dialator report good results with a low mortality rate. I have never used this instrument. Doubtless the older Bailey-type instrument was an effective dilator in opening valves but it often produced insufficiency. I wonder if some of the success of the Brock dialator is not really due to the fact that the dialator is not effective enough to open the valve and that the patient, thus avoiding insufficiency, is allowed to survive the operation.

DR. HENRY SWAN (Denver, Colo.).—I would like to agree very much with Dr. Lewis. We have had a very small experience with acquired stenosis. Actually, only 5 of our 23 or 24 patients in whom we have opened the aorta and taken a look at the aortic valve have been patients with acquired disease. These have been rather carefully selected by Dr. Blount along the lines that Dr. Lewis suggests; namely, that they have had careful x-ray studies with laminography. Thus, I have been protected from the very heavily

calcified valves. These 5 patients then represent a rather selected group of patients from a very much larger group that Dr. Blount has seen which I have not. But I have been very much pleased with the results in these 5 patients. The percentage of rehabilitation has been very marked, with loss of angina, return to fishing and hunting, vigorous exercise, full day's work, and so forth. To the patient, this is very real and, therefore, there is a very definite place for the open operation. But I also think the patients should be carefully selected so that at operation you are not looking at a calcified structure on which it does not make any difference whether you have two minutes, 20, or 2 hours, you still could not do a very good job with it.

DR. CONNOLLY (closing).—Regarding what Dr. Shaw said about dividing all three cusps, that may be correct. We just felt that in the quite severely diseased ones the most that we could do would be to raise the opening beyond the critical area of 0.75 cm^2 and we were very careful and worried about producing insufficiency. That is why in most instances we only divided two cusps. If we saw one that had a heavily calcified cusp, we would naturally cut that one among the two we were cutting. What I did want to do was make a plea that you explore the mitral valve in almost every case because it may limit your result since we found such a high incidence of concomitant mitral stenosis and it is very easy to do so.

Drs. Lewis and Swan mentioned the finding of calcium in the aortic valve by x-ray as a possible contraindication to operation. I would not agree to this since every case that we examined at the autopsy table in our series of 75 cases who died of aortic stenosis had marked calcification of the valve. Naturally, if no calcium is seen on the x-ray the chances of a relatively good valve to work with is higher but most of the patients who need help in the acquired type of aortic stenosis have large amounts of calcium in the valve.

I think the age of the patient is more important than whether you see calcium on the x-ray. In the patient over 35 years of age, the incidence of calcification of the valve goes way up so that if we can operate on them before that age we can expect a much more favorable result.

THE MANAGEMENT OF VENOUS THROMBOSIS AND PULMONARY EMBOLISM

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THE treatment of established venous thrombosis and its major complication, pulmonary embolus, remains a problem for both internist and surgeon. The evolution of the therapeutic regimen to be evaluated below is based upon the following theses: (1) that venous thrombosis, whatever its actual origin, remains a problem in intravascular clotting and must, therefore, be treated primarily with anticoagulants; (2) that ligation of the major veins remains a sure way of avoiding embolism if done high enough and soon enough, and if the ligation is supplemented by anticoagulant therapy (3) that the segregation of a source of emboli below a venous ligature does not give one license to stop treating the basic disease of venous thrombosis; and (4) that the anticoagulant of choice is heparin because of its prompt clinical response, quick initial therapeutic level, ease of control, and the safety of prompt neutralization.

A series of cases with the diagnosis of venous thrombosis was selected at random from the files of Wadsworth General Hospital, Veterans Administration Center, Los Angeles, 1953 through 1954, and the University of California Hospital, Los Angeles, 1954 through 1957. One hundred and fourteen cases were found suitable for critical review. Approximately one-half of these cases had been treated according to the criteria outlined.

Of this group, 34 cases were representative of superficial saphenous thrombophlebitis. Half of them were primary, but in the other half there coexisted some other factor, such as carcinomatosis or infection, that could have played an etiologic role. There were two nonfatal emboli among this group.

The major portion of this paper is concerned with 84 patients with deep venous thombosis of which 16 also had a superficial saphenous thrombophlebitis. Thirty-eight patients had pulmonary embolism during some part of the history.

TREATMENT

Efficacy of Anticoagulants for Thombosis.—Summarized in Table I are the data concerning 22 patients in whom there was a recurrence of venous thrombosis. In 6 instances there was manifest recurrence of thrombophlebitis while the patient was on adequate anticoagulant therapy in the hospital. Dicumarol was the agent in question in 5 instances, heparin in one. The remaining recurrences appeared after intervals of 2 days to 6 months following cessation of treatment or previous thrombophlebitic activity.

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These figures confirm my clinical observations that patients on antiprothrombin drugs did not show so prompt nor so persistent a response as did those on heparin. The total benefit to the patient by this diminished tendency to recurrence is tempered by the observations made in the next section.

TABLE I. EFFICACY OF ANTICOAGULANT THERAPY IN TREATMENT OF VENOUS THROMBOSIS

BASIC TREATMENT	NUMBER OF CASES	RECURRENCES	
		NUMBER	PER CENT
None	14	5	35*
Heparin	42	6	14
Dicumarol	24	11	45

*Several patients died without a chance to show recurrent thrombosis.

Efficacy of Anticoagulants for Pulmonary Embolism (Table II).—Ten of the patients who had pulmonary embolism were not treated by anticoagulants; all died. One of these patients had thrombocytopenic purpura, and for him anticoagulant therapy was believed to be contraindicated. He died of recurrent embolism after ligation of both superficial femoral veins. There were 4 patients of whom the diagnosis of pulmonary embolism was made but who, for various reasons, received no therapy at all. There were 3 patients who entered the hospital in a moribund condition from another cause, and, although the antemortem picture might have allowed diagnosis, treatment was not given and they succumbed to a combination of their basic disease and pulmonary embolism. There were only 2 cases that can legitimately be described as having fatal embolus without prior recognizable signs of symptoms.

TABLE II. EFFICACY OF ANTICOAGULANTS IN CONTROL OF EMBOLISM

A.				
Not treated with anticoagulants (all died)				10
Treated with anticoagulants				28
No recurrence			6	
Recurrence			22	
After treatment		4		
During treatment		18		
Dicumarol	5			
Heparin	13			
B.				
Total recurrence after initiation of anticoagulant therapy				
With Dicumarol		7/24	(29%)	
With heparin		15/42	(36%)	
Total fatal embolism after initiation of anticoagulant therapy				
With Dicumarol		1/24	(4%)	
With heparin (6 on therapy)		8/42	(19%)	

There were 28 patients with pulmonary embolus who were treated with anticoagulants. In only 6 of these was there no recurrence of embolism, either while receiving therapy or after cessation of therapy.

At first glance the figures in Table II seem to contradict those in Table I. This may perhaps be explained by the observation made earlier that heparin seemed to relieve the signs of inflammation in the presence of a venous thrombosis more promptly than did Dicumarol. It is suggested then that under

heparin therapy the clot already formed is prevented from sticking to the vein wall and the signs of thrombophlebitis are minimal, although the hazards of the loose-lying clot continue to exist. With the less effective antiprothrombin agent the clot may adhere and cause more symptoms, but it remains in a safer situation. It is true that heparin does possess certain advantages from the point of view of ease of control, safety, and reversibility which will continue to make it a valuable agent. On the other hand, it would be better if there were some means to provide a safe mechanism for controlling embolism other than the unpredictable degree of adherence of a loose clot to the vein wall.

Efficacy of Venous Ligation and Anticoagulants in Controlling Pulmonary Embolism.—On the basis of previously reported experience[2] and confirmed by current surgical reports,[1, 3, 5] it has been my policy to offer higher levels of ligation in an attempt to forestall anticipated pulmonary embolism. Table III shows the surgical experience in this group of cases.

TABLE III. RESULTS OF MAJOR VEIN LIGATIONS

SITE	NUMBER	SUCCESSES
Vena cava	4	4
Iliac vein	3	3
Femoral vein	9	6*

*Postligation failures—1 fatal embolus, 1 nonfatal embolus, in patients who had recurrent embolism on anticoagulant therapy, and 1 fatal embolus in patient who did not receive heparin after venous ligation.

Crum[4] has studied 21 cases of ligation of the vena cava. Only one of his patients had what might have been a pulmonary embolism after operation. Adding these cases to those of my present and previously reported series, there are 26 patients who have had ligations of the vena cava, mostly because of recurrent embolism or recurrent venous thrombosis, with only one postoperative embolus.

One of the chief reasons given for avoiding the vena cava as the site of ligation is the alleged late morbidity. In Crum's cases, 15 of 16 patients who were working prior to operation had returned to work, although 16 reported varying amounts of edema. Neither in the present review of cases nor in my experience outside of this review have I been able to find any case in which venous ligation, immediately supplemented by postoperative heparin and carefully progressive ambulation, had clearly resulted in more edema than had been present preoperatively. One might formulate the thesis, therefore, that the extent of edema to be expected will depend upon the amount of destruction that the main valve-protected venous channels have sustained irrespective of ligation. Indeed, some of the most recalcitrant forms of postphlebitic edema have been in those patients whose original thrombosis was a highly symptomatic one in the femoropopliteal and tibial system and who never underwent any form of ligation.

SELECTION OF CASES FOR VENOUS INTERRUPTION

Table IV is a classification of cases according to the system advocated by Crane,[3] with the addition of a group for those cases in which venous thrombosis seemed to arise spontaneously.

TABLE IV. CLASSIFICATION OF CASES FOR VENOUS INTERRUPTION

	NUMBER OF CASES	THERAPEUTIC FAILURES AS EMBOLIC DEATHS	PER CENT
Group I: Relatively young patients making otherwise uncomplicated recovery from surgery	19	1	5
Group II: Patients with serious systemic or local complications or pre-existing complicating factors	44	7	16
Group III: Patients with spontaneous venous thrombosis	8	1	13

It would seem that the suggestion made by Crane, that relatively young patients making an otherwise prompt and uncomplicated recovery from surgery who develop venous thrombosis need only the protection of a single course of anticoagulant therapy, is proper. For those surgical patients who run a complicated postoperative course, or those medical patients with a protracted illness which might serve as a continuing causative agent, or those patients who develop thromboembolism spontaneously, venous interruption is probably warranted. Ligation should be performed at as high a level as is compatible with a reasonable surgical risk. It is certainly true that many critically ill patients can tolerate bilateral femoral vein ligation under local anesthesia when they could not tolerate even the relatively quicker extraperitoneal ligation of the vena cava under general or spinal anesthesia. Venous interruption should be immediately supplemented with postoperative heparin in order to (1) continue the limitation of the thrombophlebitic process in the leg in an anticipation of preventing further late local complications, (2) reduce the risk of clotting arising in the proximal venous stream at the site of intimal injury by the ligature itself, and (3) reduce the slight risk of embolism from some source other than the venous bed not segregated below the tie. Provided that these criteria are met, little worry need be given to the risk of increasing the patient's tendency to postphlebitic edema. Venous thrombosis associated with any situation that precludes anticoagulant therapy carries a serious mortality risk and vein ligation at a high level should be offered, even though the protection afforded is not as satisfactory.[3]

SUMMARY

A survey of 80 cases of deep venous thrombosis indicates a serious failure rate in the form either of recurrent venous thrombosis or of originally occurrent or recurrent pulmonary embolism treated by anticoagulants. Heparin seemed more effective than Dicumarol in relieving the symptoms of venous thrombosis, but heparin therapy was associated with a number of fatal pulmonary emboli in the presence of what appeared to be adequate therapy. Venous ligation, especially at the level of the vena cava when tolerable by the patient and when supplemented by postoperative anticoagulant therapy, seemed to offer the safest course with minimal morbidity.

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Discussion

DR. W. ANDREW DALE (Nashville, Tenn.).—Dr. Barker, I was concerned by the recurrence rate which you reported and would like to ask the length of time of use of anticoagulants and also whether the selection of a series might have anything to do with this.

I would like to ask whether you have seen any of a particular complication which has occurred recently three times in our experience and which is either not reported in the literature or is poorly reported; namely, that of bronchopleural fistula occurring secondary to the breakdown of the infarct due to a pulmonary embolism. The first case that we saw occurred in a patient with a rectal carcinoma who had a vena caval ligation which prevented further embolism, but he did break down an infarct and subsequently died, not only due to his carcinomatosis, but probably a widespread empyema hastened the process. The second patient had had a Teflon bifurcation graft successfully placed for a ruptured aneurysm. He returned 3 months later with a peculiar syndrome of bilateral pleural fluid, coughing up blood, and some opacities in the lung. It was finally determined that he had a pulmonary embolism. His infarct eventually also ruptured and he developed air within the chest on the left. This was successfully managed by placing a tube into the left chest and connecting it to negative suction drainage.

The third patient I would like to illustrate by a slide. This illustrates a patient who had a fractured femur in September, 1956. After intramedullary nailing in October, he was sent home. He developed phlebitis on November 20, was treated in another hospital with Dicumarol therapy, developed pulmonary embolism, and was admitted to our hospital. We are probably becoming increasingly conservative toward continuing anticoagulants rather than performing a caval ligation and continued the patient on Coumadin wondering if he might develop a bronchopleural fistula. This developed on the first of January, necessitating a 1,000 c.c. blood transfusion because of tremendous loss into his chest. Closed chest catheter drainage was begun and, some 5 days later, operative decortication was performed. We continued the Coumadin postoperatively and, when seen a few weeks ago, this patient was in good condition. I have seen three of these bronchopleural fistulas recently and suspect others share this experience.

DR. CHILTON CRANE (Boston, Mass.).—Dr. Barker's excellent paper brings up once again the problem of pulmonary embolism, and I am sorry that Dr. Richard Warren could not be here today to comment. At any event, in his behalf, I did want to report very briefly a case of massive pulmonary embolism recently successfully treated surgically by him and the resident staff at the Peter Bent Brigham Hospital.

The patient was a 65-year-old woman, 6 days postcholecystectomy, who suffered sudden syncope while walking on the ward. The blood pressure was at first unobtainable but soon returned to 90 systolic, while the pulse remained very weak and thready. There were no leg signs. The ECG, 10 minutes after onset of symptoms, showed right bundle branch block. During transportation to the operating room, the respirations became rather gasping in type. Thirty-five minutes after onset of symptoms, the chest was opened without need for anesthesia; the heart was beating feebly with much dilatation of the right side. The pulmonary artery was opened, no clot was obtained from the left main pulmonary artery, but (slide) the large clots you see there were removed from the right pulmonary artery.

It then required about 30 minutes to resuscitate the heart, but following this the patient made a good recovery except for transient ECG changes suggesting posterior myocardial infarction. The patient is now 5 months postoperative and in general she has done very well. I think that you are all familiar with the fact that the world literature records some 13 or 14 cases of successful pulmonary artery embolectomy, but, as far as is known, we believe this to be the first such case to be reported in this country.

DR. WILLIAM G. ANLYAN (Durham, N. C.).—We have had a very similar experience at the Drake University Hospital except for the complications on the heparin therapy reported by Dr. Barker. We have come to the following conclusions: that anticoagulant therapy with a combined heparin and coumarin regimen is the treatment of choice; and that a patient with pulmonary embolism should be maintained on subcutaneous heparin therapy only for 8 days followed by several weeks of coumarin therapy until normal activity and ambulation is resumed. We prefer vena caval ligation in patients with concomitant active bleeding such as following prostatectomy and in patients with repeated embolism despite multiple courses of anticoagulant drugs. Finally we advocate the performance of thrombectomies with simultaneous heparin therapy in young patients with massive thrombosis.

DR. BARKER (closing).—It seems clear that there are considerable differences of opinion regarding many aspects of this problem.

Dr. Dale questioned the length of time that our patients had been on heparin therapy. Two patients who had massive recurrent embolism did so within 48 hours of the initiation of their treatment. Other than that, the time of recurrence was in a completely random pattern. There were several patients who suffered recurrent embolism after adequate levels of heparinization for 21 to 28 days.

As far as selection of patients by sampling is concerned, these patients represent all of those whose charts were available for study, with adequate follow-up data, over the selected period of time. This group may certainly have been preselected insofar as those patients with complications may have tended to maintain contact with the Veterans Administration and stayed around to provide us with an adequate follow-up.

We have not encountered any instances of bronchopleural fistula.

Drs. Warren and Crane must certainly be complimented for their effective application of the direct attack on the pulmonary embolus itself.

(End of Society for Vascular Surgery papers.)

HEMORRHAGIC DIATHESIS ASSOCIATED WITH MASSIVE TRANSFUSION

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AN UNEXPLAINED bleeding tendency in the surgical patient is not new in clinical experience. In the past decade, however, with the increasing frequency of large-scale operations and the use of large volumes of blood for replacement, fatal hemorrhage of obscure origin has raised challenging questions. During the Korean conflict this complication was noted in field and forward hospital surgery.[13] The syndrome became known as "hemorrhage due to massive transfusion" and serious indictment of large volume blood transfusion excited general concern. Investigators probed the possible defects in the biochemical coagulation mechanism caused by large volume transfusions. Studies to date, however, have not indicated a common cause for the abnormal bleeding. It would appear from our experience that massive transfusion was implicated by association rather than being primarily causal.

The opportunities to study this phenomenon in man are limited by lack of clinical material. Krevans[9] studied 11 cases and indicated thrombocytopenia to be causal. Cliffton and associates[4] have drawn attention to abnormalities of the fibrinolytic system in their cases. Zucker[18] found a high correlation between multiple defects and bleeding. Bunker[3] showed that the occurrence of citrate toxicity was a function of rate of infusion of citrated blood. Howland[7] recently confirmed this observation.

Open cardiac surgery with its concomitant need for massive blood replacement presented a unique opportunity to study this problem. In this paper, we report the results of study of 38 patients who received large volume blood replacement. Of 30 patients who were subjected to open cardiac surgery, 8 bled abnormally. Eight patients who had closed cardiac surgical procedures and who bled abnormally are also considered.

The purpose of this paper is to consider three questions: (1) Is the abnormal bleeding due to massive transfusion or vice versa? (2) Is there a common cause for the observed hemorrhage which is not only necessary but sufficient? (3) Does such a defect, if present, reside in the fluid compartment of the blood, the platelets, the vasculature, or combinations of these?

MATERIALS AND METHODS

Unless otherwise indicated all methods are those to be found in the book *Blood Coagulation—Methods of Study* edited by L. Tocantins.[15]

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The following studies were performed on each sample of blood.

Platelet count (wet method employing isotonic 1 per cent EDTA solution as diluting fluid)
Thromboplastin generation test[2] with lipid substitute[1] for platelets
Prothrombin consumption test[10]
Factor V[14] (labile factor, accelerator globulin)
Factor VII[5] (stable factor, S. P. C. A.)
One-stage prothrombin modified[11]
Fibrinogen[12]
Plasma recalcified clotting time[2] (calcium clotting time)
Test for inhibitors (the prolongation of the recalcified plasma clotting time of normal plasma by an equal volume of patient's plasma)

Fibrinolysin Assay.—Complete lysis of endogenous fibrin in the plasma recalcified clotting time sample was taken as the initial crude indication of fibrinolysin. Complete lysis at 37.5° C. in less than 4 hours was interpreted as evidence of a strong lysin, complete lysis of fibrin in more than 4 hours as evidence of a weak lysin, and complete lysis of endogenous fibrin in more than 24 hours as evidence of negligible or absent fibrinolysin.

Operative Sampling and Analytic Procedures.—The candidate for open heart surgery was brought to the operating room at which time a sample of blood was obtained and processed as will be described. Then bilateral cutdowns were made and citrated bank blood was started. After thoracotomy and isolation of the femoral artery and vein (for cannulation in conjunction with the heart-lung bypass), a second sample was taken for analysis of blood coagulation components. Then the heart and lungs of the patient were excluded from the corporeal circulation and the pump-oxygenator was started. Heparinized blood (15 mg. per 500 c.c.) 12 to 18 hours old was used. The pump-oxygenator contained approximately 2 L. of whole blood and maintained a venous reservoir of from 1 to 2 L. of blood. Immediately prior to the heart-lung bypass, heparin (1.5 mg. per kilogram of body weight) was injected intravenously. The heart-lung bypass was operative from 5 to 15 minutes in the earlier cases and from 15 to 60 minutes during the latter cases of this series. In some latter cases of this series, potassium citrate cardiac arrest was utilized. Immediately after the bypass procedure was finished, the thoracic cavity was closed, bilateral thoracotomy drain tubes were left in place under constant low pressure suction, and protamine or Polybrene[16] was added to neutralize the heparin, a third sample was taken for blood coagulation analysis. Subsequent samples taken at 2 hours postoperative and 24 hours postoperative were analyzed for blood coagulation components.

Procedure for closed cardiac surgery: The blood used in these patients was citrated bank blood. Other than the use of heparinized blood in the coronary endarterectomy case, no obvious significant manipulative procedures relative to the purpose of this study were performed. All samples obtained on this group of patients were postoperative samples.

Sampling procedure: At the time or intervals indicated above, blood was drawn by clean venipuncture into siliconized syringes. The blood was then placed immediately into siliconized test tubes containing one-ninth volume of 3.8 per cent sodium citrate solution or into glass test tubes. At this time information on the amounts of blood used and other pertinent data were obtained from the anesthesiologist. The samples were analyzed immediately or frozen at −10° to −15° C. for subsequent analysis. Platelet counts were started within 10 minutes of collection. As indicated previously the initial sample (I) was a preoperative sample taken before thoracotomy, the preshunt sample (Pre) was taken after thoracotomy but before bypass, and the postshunt sample (Post) was taken after the bypass and after Polybrene had been given or, in earlier experiments, protamine had been added to neutralize the heparin. The 2 (+2) and 24-hour (+24) samples were taken in the same manner. The site of obtaining blood from the patient in the early part of the series was direct cardiac puncture; during the middle and latter parts of the study the antecubital fossa and infrequently the femoral artery or vein were used. During the course of the operations, the external jugular vein was utilized occasionally as a site for obtaining blood samples in exceptional cases.

DEFINITION OF MASSIVE TRANSFUSION

Massive transfusion means the administration of more than 5 pints of whole blood within a 24-hour period.

DEFINITION OF BLEEDERS

The criteria for inclusion of a patient in this category for the purposes of this study were as follows: (1) Usual measures to control bleeding at the operative site were inadequate; abnormal oozing definitely was noted by the surgeon. (2) Volumes of blood loss were in excess of that usually expected for the procedure. (3) Blood replacement was in excess of what is usual for the procedure. (4) Postoperative incisional hematoma, ecchymosis, purpura, and unusually large amounts of blood loss by drainage tubes were seen.*

RESULTS

In Table I is shown a compilation of some data on the patients studied. The patients have been divided into three groups. The first group is composed of those patients who underwent open heart surgery and who subsequently did exhibit a hemorrhagic diathesis (bleeders). The second group comprised those patients who underwent open heart surgery but who did not bleed (nonbleeders). This group served as an important control in the study. The third group was made up of those patients who underwent closed heart and noncardiac procedures. The patients in this latter group were studied because all exhibited a hemorrhagic syndrome. Examination of the weight, age, sex, and type of pathology present as listed in Table I does not reveal any obvious significant differences between the three groups.

An examination of the volumes of blood employed for the different groups is of interest. In Table I are listed the total volumes of blood received by the individuals in this study. It is to be noted that all 22 patients undergoing open heart surgery and who did not bleed had over 3 L. of blood usually in less than 10 hours. Further, 6 of these patients had over 5.4 L. of blood in 7 hours or less. None showed a hemorrhagic manifestation. In Table II is shown the calculated amount of blood received by bleeders on open heart surgery up to the time hemorrhage started. In Table III is a similar compilation of data for bleeders on closed heart surgery. The key data are shown in summary form in Table IV. Here it may be seen that the average total volume of blood received by each group of bleeders (9.5 L. and 9.0 L.) is approximately 1.7 times that received by the nonbleeders.

An examination of the second row of figures in Table IV shows that at the time of hemorrhage, the bleeders had received 6.0 and 4.6 L. of blood, respectively, with an average volume of 5.3 L. It is noteworthy that this is the same average volume of blood given to 19 of 22 patients who did not bleed. Thus, 16 patients received an average of 5.3 L. at which time they started to bleed. Nineteen patients received an average of 5.4 L. without any manifestations of a hemorrhagic diathesis.

*Bleeding cases due to technical errors were excluded.

TABLE I

EXPERIMENT NUMBER	TIME OF TRANSFUSION	MAXIMUM RATE (C.C.)	VOLUME	HEPARIN OR CITRATE	AGE, WEIGHT & SEX	TYPE OF OPERATION & PATHOLOGY	LENGTH OF TIME ON SHUNT	MORTALITY*	CAUSE OF DEATH
OPEN HEART SURGERY									
Bleeders									
4	12 hr.	600/hr.	2 Fr. I & 6,500	H & C	45-160-M	Open A.S. & A.I.			
5	15 hr.	1,250/hr.	7,000	H & C	18-156-M	Open hypothermia I.V.-S.D.	14 min.	–	
6	5 hr.	800/hr.	4,000	H & C	45-135-M	Open A.S.	15 min.	–	
17	12 hr.	800/hr.	10,000	H & C	43-191-M	Open A.S.	21 min.	+	7 days postop. pseudomonas infection
23	10 hr.	1,510/hr.	1 Fr. I 8,200	H & C	52-161-M	Open A.S.	30 min.	+	4 days postop. pseudomonas infection
24	34 hr.	2,500/hr.	1 Fr. I 21,000	H & C	49-152-M	Open A.S.	20 min.	+	4th day cerebral anoxia and renal failure
33	6 hr.	1,800/hr.	8,350	H & C	32-136-M	Open A.S.	25 min., 30 sec.	+	3 hr. postop. hemorrhage from aortic sutures
50	7 hr.		1 Fr. I 10,700	H & C	37-110-F	Open A.S., died in operating room	70 min.	+	Hemorrhage from aortic suture lines
Nonbleeders									
2	24 hr.	500/hr.	11,000	H & C	55-165-M	Open A.S.	15 min.	–	
8	4 hr.	1,000/hr.	6,000	H & C	43-163-M	Open A.I.	23 min.	+	Ventricular failure following massive hemorrhage from aorta
9	10 hr.	350/hr.	3,500	H & C	44-168-M	Open A.S.	19 min.	–	
13	4 hr.	1,000/hr.	3,500	H & C	18-M	Open A.S.	33 min.	+	6th day pseudomonas septicemia

A.S.—Aortic stenosis.
A.I.—Aortic insufficiency.
I.V.S.D.—Interventricular septal defect.
M.S.—Mitral stenosis.
I.A.S.D.—Interatrial septal defect.
Fr. I—Fraction I of Cohn: fibrinogen and antihemophilic globulin.
*Mortality—+ = died; – = lived.

TABLE I (CONT'D)

EXPERIMENT NUMBER	TIME OF TRANSFUSION	MAXIMUM RATE (C.C.)		VOLUME	HEPARIN OR CITRATE	AGE, WEIGHT & SEX	+	TYPE OF OPERATION AND PATHOLOGY
18	2 hr.	1,750/hr.	3,500 H & C	59-139-M	Open A.S.	11 min.	+	Hemorrhage from right atrium, ventricular fibrillation during closure
22	4 hr.	750/hr.	3,000 H & C	52-150-M	Open A.S.	15 min.	−	
34	5 hr.		5,100 H & C	25- 90-F	Open M.I.	26 min., 11 sec.	+	Ventricular fibrillation during closure
35	7 hr.		4,000 H & C	41-130-F	Open M.I.	21 min.	+	5½ hr. postop. hypotension
36	7 hr.	800/hr.	5,500 H & C	44-158-M	Open A.S.	15 min.	+	Hemorrhage from ruptured spleen
37	4 hr.		7,500 H & C	M	Open M.I.	26 min., 28 sec.	+	Exsanguination during surgery
38	7 hr.	700/hr.	4,725 H & C	58-160-M	Open A.S.	10 min., 45 sec.	−	
39	7 hr.	900/hr.	6,500 H & C	15-105-M	Open I.V.S.D.	31 min., 43 sec.	−	
40	5 hr.		3,200 H & C	48- 92-F	Open A.S. & M.S.	9 min., 20 sec.	+	14 hr. postop. mesenteric & cerebral thrombosis
41	72 hr.	6,900/7 hr.	8,900 H & C	63-158-M	Open A.S.	15 min., 33 sec.	−	Discharged improved, died 8 mo. later, aortic insufficiency
42	7 hr.		5,500 H & C	53-144-F	Open A.S.	35 min.		
43	7 hr.		7,000 H & C	55-121-M	Open A.S.	28 min., 10 sec.	+	Bilateral lower lobe atelectasis
44	7 hr.		4,350 H & C	51-154-M	Open A.S.	37 min., 7 sec.	−	
45	7 hr.		3,400 H & C	36- 92-F	Open A.I.	46 min., 9 sec.	−	
46	18 hr.	3,800/6 hr.	4,800 H & C	37-151-M	Open A.S.	25 min.	−	
47	8 hr.		4,750 H & C	49-105-F	Open I.A.S.D.	38 min.	+	Died 7 hr. postop. A.V. block, prolonged hypotension, myocardial failure

48	10 hr.	4,300/5 hr.	4,800	H & C	41-136-M	Open A.S.	33 min.	–	Died after discharge, 6 wk. postop. staphylococcal septicemia and endocarditis
49	14 hr.	3,500/7 hr.	4,000	H & C	35-177-M	Open A.S.	22 min., 50 sec.	–	
CLOSED HEART AND OTHER OPERATIONS									
Bleeders									
11		72 hr.	1,500/day		3,100	C		59-107-F	Closed M.S., T.S.
12		96 hr.	1,800/hr.		6,500	C		31- 92-M	G.I. surgery, extensive
25		14 hr.	700/hr.		10 000 2 Fr. I	C		43- 96-F	Closed I.A.S.D.
27		24 hr.	350/hr.		8,500	H & C		37-140-M	Closed coronary endarterectomy
28		70 hr.	1,600/hr.		1 Fr. I 15,000	C		46-116-F	Closed I.A.S.D.
29		48 hr.			11,500	C		49-156-F	Lobectomy
30		36 hr.	660/hr.		5,000	C		33-170-M	Radical pericardiotomy pneumonectomy
51		48 hr.	5,900/hr.		11,900	C		48-123-F	Closed M.S.

TABLE II. CALCULATED VOLUME OF BLOOD RECEIVED BY OPEN HEART BLEEDERS AT TIME OF HEMORRHAGE

EXPERIMENT NUMBER	TIME BLEEDING STARTED		VOLUMES OF BLOOD GIVEN			CALCULATED AVERAGE VOLUME AT TIME BLEEDING BEGAN (C.C.)
	BEFORE BLEEDING	AFTER BLEEDING	BEFORE BLEEDING (C.C.)		AFTER BLEEDING (C.C.)	
33	1:30 P.M.	– 3:50 P.M.	6,350	–	8,350	7,350
50	12:50	– 3:30	5,450	–	8,500	7,000
4	Before	– 7:30 P.M.		–	6,500	6,500
5	2:30 P.M.	– 2:15 A.M.	4,000	–	7,000	5,500
6	Immed. postop.			–	4,000	4,000
17	1:45	– 3:30	3,000	–	5,000	4,000
23	11:25 (During shunt)	– 1:15	1,000 + = ?	–	5,750	5,750
24	1:55	– 4:20	5,750	–	9,750	7,750
	Grand average					5,970
	Extremes absolute		3,000	–	9,750	
	Extremes average		4,450	–	7,390	

TABLE III. CLOSED HEART PATIENTS STUDIED TWO HOURS POSTOPERATIVE

EXPERIMENT NUMBER	VOLUMES OF BLOOD GIVEN WHEN BLEEDING BEGAN (C.C.)
25	(3,500-4,500)
28	2,000
29	7,000
30	4,000
51	more than 5,900
Average	4,600

TABLE IV

	OPEN HEART		CLOSED HEART
	NONBLEEDERS (19)	BLEEDERS (8)	BLEEDERS (8)
Total blood given			
Means	5,400 c.c.	9,500 c.c.	9,000 c.c.
Extremes	3,000-11,500 c.c.	4,000-21,000 c.c.	3,100-15,000 c.c.
Blood given up to time of hemorrhage			
Means		6,000 c.c.	4,600 c.c.
Extremes		4,000-7,750 c.c.	2,000-7,000 c.c.

Platelets.—Fig. 1 shows the platelet values for the group of 30 patients during the course of open heart surgery and the postoperative period. The means and standard deviations are indicated. It is to be noted throughout the course of these studies that samples are occasionally lacking for some patients in the time intervals designated. The curve at the top of Fig. 1 is representative of the open heart surgical group as a whole (bleeders and nonbleeders). A progressive drop in platelet count up to the immediate postoperative period is demonstrated. The platelet level was then maintained to 24 hours postoperatively at a level approximately one-half of the preoperative value of 250,000 platelets per cubic millimeter. In the lower part of Fig. 1 are curves representing the platelet levels of bleeders and nonbleeders, respectively. The values are different in the following respects. The bleeders' platelets are initially somewhat higher and ultimately somewhat lower than that of nonbleeders. Thus, the drop of platelet count over 24 hours was significantly greater for the group of bleeders than for the nonbleeders ($p = 0.05$). It is of much interest that the absolute level of platelets at the postoperative and 2-hour postoperative period was not significantly lower in bleeders than in nonbleeders, for it was at this time that the hemorrhagic syndrome usually manifested itself in our group of patients.

Recalcified Clotting Time.—In Fig. 2 are shown the values of the recalcified plasma clotting times. The curve at the top of the figure represents the group as a whole (bleeders and nonbleeders). There was a progressive and steady prolongation of the clotting times over the intervals studied. The 2-hour postoperative and 24-hour postoperative values are significantly longer than the initial value ($p < 0.02$). The curves at the bottom of Fig. 2 represent the bleeders and nonbleeders, respectively. The same general tendency is exhibited by both groups. Analysis, however, indicated that, at the 2-hour postoperative and 24-hour postoperative times, a significant prolongation in bleeders' clotting time with respect to the initial values occurs. This is not true for the nonbleeders.

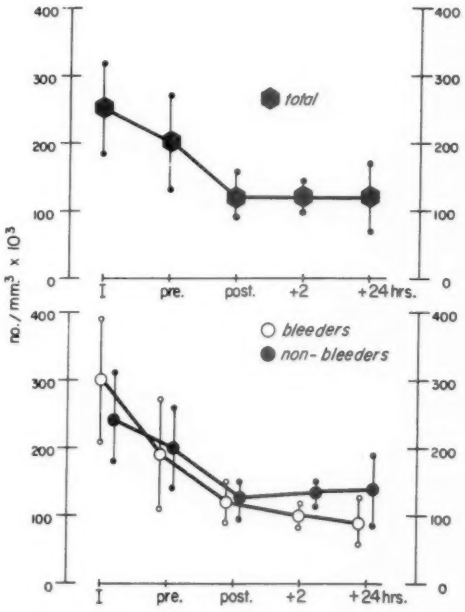

Fig. 1.—Platelets. Absolute values.

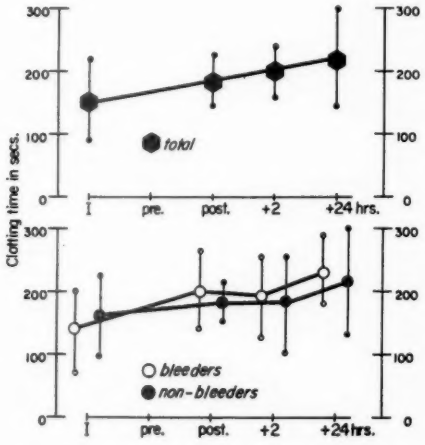

Fig. 2.—Absolute recalcified plasma clotting times.

(Figs. 1, 2, 3, 5, and 6 from Ulin, Gollub, Winchell, and Ehrlich: Hemorrhage and Massive Transfusion, J. A. M. A. **168**: 1971-1973, 1958.)

Thromboplastin Generation Test.—At the top of Fig. 3 is shown the curve for the thromboplastin generation test (T.G.T.) for the group as a whole. There is a postoperative depression in the values with a slow return toward normal thereafter. In the lower half of the figure are plotted the values for bleeders and nonbleeders, respectively. The same general tendency is exhibited by both groups. The differences between bleeders and nonbleeders are not significant from the statistical point of view.

Prothrombin Consumption.—In Fig. 4, at the top, is shown the mean and standard deviation of the prothrombin consumption values for the combined group of patients undergoing open heart surgery. There is a slight decrease in prothrombin consumption at the postoperative period with a return toward the initial value subsequently. The postoperative fall is not considered significant. At the bottom of the figure are shown the curves for bleeders and nonbleeders, respectively. The curves are in general quite similar and the differences in means are not considered significant.

Prothrombin Time.—Fig. 5 shows the values for the one-stage prothrombin time test. In the upper part of the figure is shown the curve for the group as a whole. There is a fall from the initial value of 84 per cent to a value of 60 per cent in the postoperative period with a slow return toward normal thereafter. The difference between the initial and postoperative sample is highly significant statistically ($p < 0.01$). The same is true for the

difference between the initial and the 2-hour sample. In the lower part of the figure are shown the curves for the bleeders and nonbleeders, respectively. The curves are similar and such differences in means as are observed are not considered significant.

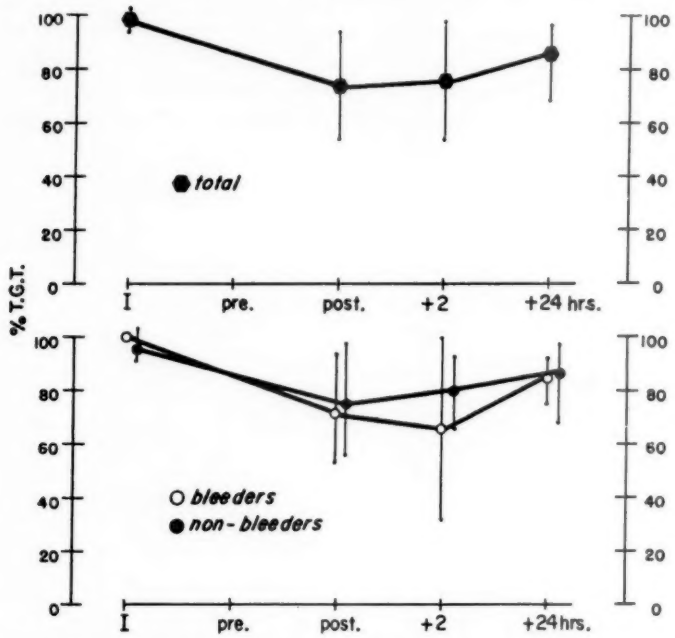

Fig. 3.—Thromboplastin generation test (T.G.T.). Absolute values.

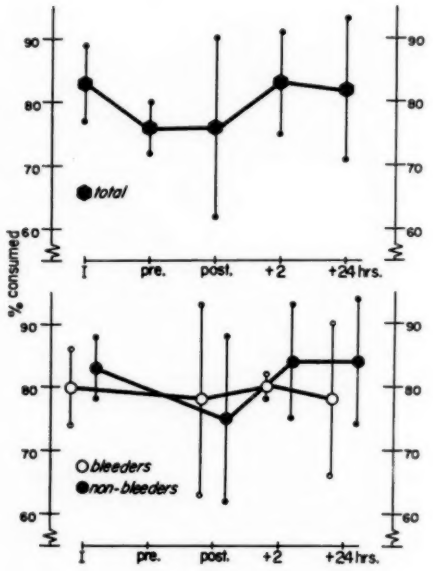

Fig. 4.

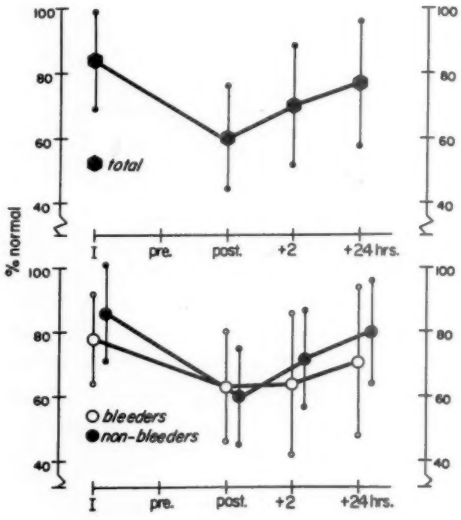

Fig. 5.

Fig. 4.—Prothrombin consumption. Absolute values.
Fig. 5.—One-stage prothrombin time test. Absolute values.

Fibrinogen.—In Fig. 6 are shown the values of fibrinogen for the group of 30 patients undergoing open heart surgery. The curve at the top is representative of both bleeders and nonbleeders. There is a loss of approximately 100 mg. per cent fibrinogen up to the postoperative period. A striking increase in the mean value at the time of the 24-hour sample

is in evidence. Statistical analysis indicates that the initial postoperative and 24-hour postoperative samples are significantly different from each other ($p < 0.01$). In the lower part of the figure are shown the curves for bleeders and nonbleeders, respectively. The curves are in general quite similar and such differences in means between bleeders and nonbleeders as are observed are not considered significant.

It was of interest to determine how the bleeders' values were distributed in the range of values of the entire group. It was further considered of interest to determine whether there was a shift in the relative position of bleeders' values throughout the range of values as the operative and postoperative period progressed.

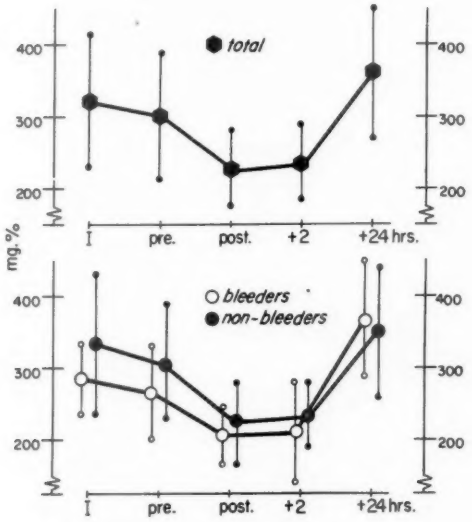

Fig. 6.—Fibrinogen. Absolute values.

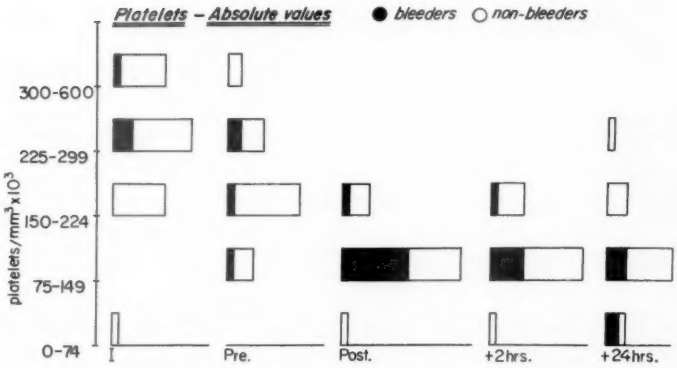

Fig. 7.—Distribution of bleeders' and nonbleeders' platelet values (absolute).

In Fig. 7 is shown the distribution of bleeders' and nonbleeders' platelet values. The time periods are the same. The values represented in the ordinate have been divided into classes. The bleeders are represented by the dark part of the bar graphs which project from left to right for each particular time of analysis. It may be seen that the bleeders' platelets are distributed in the upper range of values initially. It is of some significance that at the postoperative and the 2-hour postoperative time, the bleeders' platelets are found in the mean and upper levels of distribution. As has been pointed out before, this interval corresponds to the time when bleeding usually was manifest. As time progressed the bleeders' platelet values became distributed in the lower portion of the range of values.

In Fig. 8 is plotted the distribution of the recalcified plasma clotting time values of bleeders and nonbleeders in a similar manner. Here again, an interesting and provocative trend appears; the bleeders initially were in the shorter clotting time ranges and as time progressed the relative distribution of bleeders steadily changed toward the longer clotting time ranges. One again notes that at the postoperative and 2-hour postoperative period the values of bleeders are fairly coextensive with that of nonbleeders. Among the 30 patients undergoing open heart procedures, 14 exhibited a fibrinolysin titer at some time during the course of the study. Eleven of these patients were nonbleeders. Of these 11 patients, 2 exhibited a strong lysin titer (lysis of endogenous fibrin in less than 4 hours) and one of these exhibited a very strong lysin titer. In this latter case a low value of 138 mg. per cent fibrinogen was achieved transiently in the postshunt sample. The other 3 patients exhibiting a fibrinolysin titer were bleeders; 2 had strong lysin titers (lysis of endogenous fibrin in one hour or less). One of these patients' samples showed a consistent and progressively stronger titer during the course of this study; lysis of endogenous fibrin

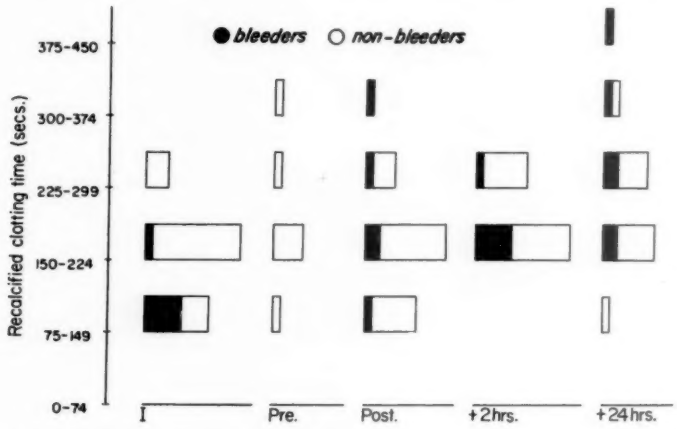

Fig. 8.—Distribution of the recalcified plasma clotting time values (absolute) of bleeders and nonbleeders.

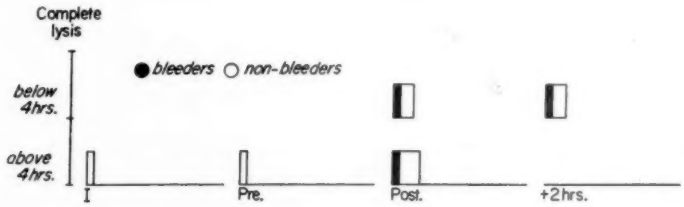

Fig. 9.—Fibrinolysin titers observed in the group of patients undergoing open heart surgery.

occurred by 18 hours, 2½ hours, and 20 minutes, respectively, for the initial, postoperative, and 24-hour postoperative sample. The fibrinogen levels of this case (Case 33) correlates in general with the lysin titers. The values were 260 mg. per cent, 155, and finally 88 mg. per cent. The other case (Case 24) had an acute afibrinogenemia manifested immediately postoperative and 2 hours after a previous value of 287 mg. per cent. Associated with this afibrinogenemia was a lysin titer of 15 minutes or less on endogenous fibrin and 2 hours and 20 minutes on exogenous fibrin. The patient manifested excessive oozing from all surfaces of the myocardium according to the surgeon. There was a laboratory response to the intravenous administration of 2 units (approximately 5 Gm.) of fibrinogen, although all signs of bleeding did not cease until an hour or more later. Thus, in summary, the incidence of patients showing fibrinolysin titer was proportionately equal in the group of bleeders and in the group of nonbleeders. One case of consistently increasing fibrinolysin titer and one case of acute severe fibrinolysin titer were found in bleeding patients. Fibrinogen values correlated well in both of these cases.

In Fig. 9 are shown in graphic form the fibrinolysin titers observed in the group of patients undergoing open heart surgery. In the postoperative period the incidence of positive titers increased markedly, and both weak and strong titers were evidenced by bleeders and nonbleeders alike.

Results on Patients Undergoing Closed Heart and Noncardiac Operative Procedures.—These data are considered separately since the operative procedures were different, heparinized blood was not used, and the heart-lung machine was not used during the course of the procedure. Moreover, the number of samples obtained on these patients was meager, inasmuch as it was not our policy to routinely follow such patients. It is to be emphasized that all the patients in this group had started to bleed before the samples were drawn. Thus, no control sample is available for this group. It is to be further noted that all patients were bleeding at the time samples were drawn.

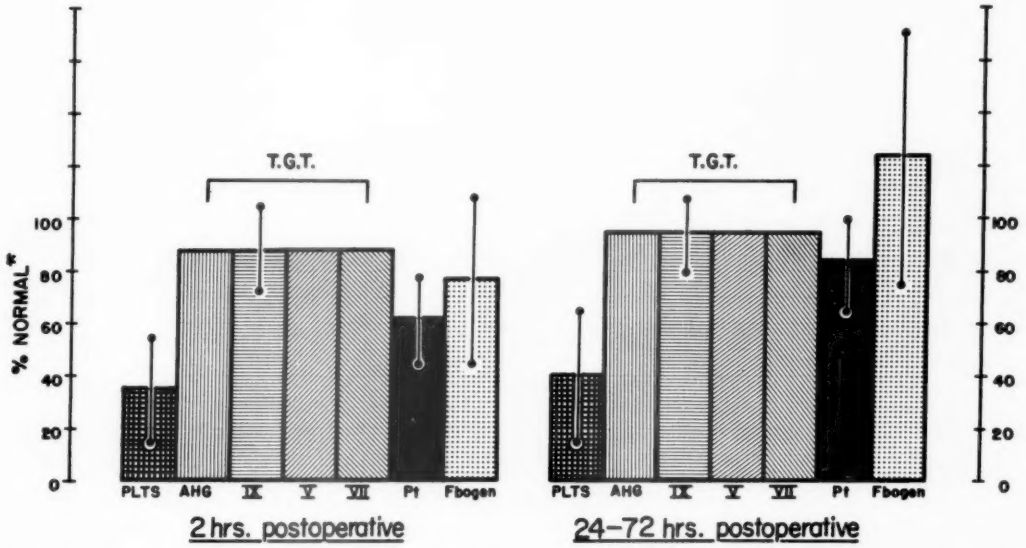

Fig. 10.—For explanation, see text. Consider 300,000 platelets (plts)/mm.^{3} = normal and 300 mg. % fibrinogen (Fbogen) = normal.

The data have been put in the form of two coagulographs (shown in Fig. 10). We have found this a useful form for quickly summarizing blood coagulation studies. Each individual bar represents a coagulation component. Those at the left of the group are thought to function early in the coagulation schema (platelets, antihemophilic globulin, and so forth). Those to the right are thought to function later in the coagulation process (prothrombin, fibrinogen). The values are expressed as percentages of normal. By 100 per cent normal platelets and 100 per cent normal fibrinogen are meant 300,000 platelets per cubic millimeter and 300 mg. per cent fibrinogen. The first coagulograph represents the average values of 5 patients who received from 4 to 7 L. of blood up to 2 hours postoperatively (Table III). Standard deviations are indicated in the figure. Of much significance was the absence of correlation between volumes of blood administered and the test values of this group. The second coagulograph (Fig. 10) represents the average values of the original 5 patients plus an additional 3 patients. This group received from 3 to 15 L. of blood up to 24 to 72 hours postoperative when they were studied. Again, there was absence of correlation between volumes of blood received and coagulation test values. Patient 11 manifested a constant but slow oozing from the operative site as well as petechiae and purpura. It is interesting to note that the total volume of transfusion was only 3,100 c.c.

The outstanding findings of this group are the thrombocytopenia manifested 2 hours postoperative and the marked fibrinogen rebound at 24 to 72 hours postoperative. The average

platelet values of the "closed" group of bleeders at 2 hours postoperative correspond remarkably with the average platelet value of the "open" group of bleeders at 2 hours postoperatively: 110,000 and 103,000 per cubic millimeter, respectively. The same is true of the 24-hour values of platelets for the "closed" and "open" group of patients. Indeed, this close agreement between the groups also was obtained for the average fibrinogen levels at both time periods, as well as levels for almost all other components. The remarkable 24-hour rise in fibrinogen was evident in both groups as well as in the nonbleeders. Finally, it should be pointed out that only one strong positive fibrinolysin result was obtained in the group undergoing closed heart operative procedures and this occurred in a patient 2 hours postoperatively who received an intermediate amount of transfused blood, namely, 4.8 L. Positive fibrinolysin assays were absent in the 24- to 72-hour postoperative sample.

Comment.—In the previous consideration of results, average absolute values of groups of patients were examined for similarities and differences. The results were not significantly different when the data were calculated in terms of percentage of initial values for each individual "open" patient and the averages compared. It was instructive to consider the results when each patient's findings were separately analyzed and the outstanding defects in each case of bleeding were noted. A summary of such considerations revealed that the outstanding defects compatible in each case with a bleeding diathesis included 2 cases of thrombocytopenia, one case of intravascular coagulation, 2 cases of fibrinolysin, one acute antihemophilic globulin deficiency, one hypoprothrombinemia, and one patient having no outstanding defect. It is obvious that the defects embrace every stage of the blood coagulation process.

DISCUSSION

The first question posed was whether massive transfusion was related to the hemorrhage in a causal or derivative manner, that is, did these patients bleed because they received massive transfusion, or did they receive massive transfusion because they were bleeding? We would like to define "cause of bleeding" as a "necessary and sufficient" condition leading to the production of hemorrhage. Data presented in Tables I, II, and III and summarized in Table IV lead to the following significant conclusions:

1. Twenty-two patients received more than 3 L. of blood in less than 10 hours for the most part and, of these, 6 patients had over 5.4 L. of blood in less than 7 hours. None exhibited a bleeding syndrome.

2. It was a fact that bleeders received a greater average total amount of blood compared with nonbleeders. However, up to the time when bleeding started, the group of bleeders did not receive more blood than the nonbleeders. Thus, bleeders had 6.0 L. and 4.6 L. to the time of bleeding. Nonbleeders received an average of 5.4 L. Thus, a significant number of patients had received massive transfusion without manifesting a hemorrhagic syndrome. The volume of blood given to patients who did subsequently bleed did not exceed the volume of blood given to nonbleeding patients. It would appear, therefore, that massive transfusion is not a sufficient condition for the production of the observed hemorrhage. A further point, frankly speculative, may be in order. It is common experience among surgeons to encounter a very infrequent patient who will exhibit signs of oozing following simple operative procedures, such as

laparotomy, in the absence of any transfusion or at most 1 or 2 bottles. Is this part of the same syndrome of "unexplained bleeding in the surgical patient" which appears in an aggravated form when larger volumes of transfused blood are used? We have no answer at present to this question and merely raise it for provocative purposes.

The next question to be considered is that of the hemostatic defect found in the bleeders. Basically, the problem under investigation is the condition of "unexplained bleeding in the surgical patient." For purposes of orientation, the diagram of Fig. 11 has been of aid. Functional hemostasis depends upon the integrated working of three components: the platelets, the plasma coagulation factors, and the intact vasculature. Impairment of any of these, as well as of combinations, may lead to hemorrhage. Such impairment may have its origin in secondary factors intrinsic to the organism (hypersplenism, fibrinolysin) or extrinsic to the organism (toxins, dilution effects). It is clear that impaired hemostasis, regardless of type or origin of secondary deleterious agents, must exhibit impairment in the integrated workings of one or more of the three basic components of platelets, plasma factors, and the blood vasculature. Studies presented herein to date bear on two of these components, namely, plasma coagulation factors and platelets. It is to be noted that the vasculature has not been studied yet.

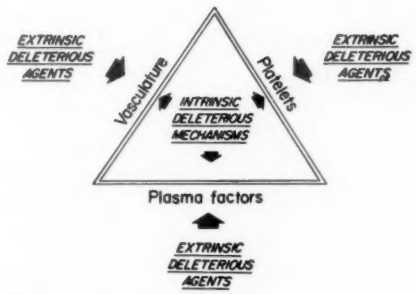

Fig. 11.—Gross anatomy of the etiology of hemorrhage.

When one examines the data of the group of patients undergoing open heart procedures to determine the changes in the blood coagulation mechanism, three procedural events immediately confuse the analysis. These were the use of inadequately heparinized and partially clotted blood in the heart-lung machine, the effect of the heart-lung machine on coagulation factors of the blood, and the use of heparin and heparin antagonists (protamine and Polybrene)[16] in conjunction with the use of the heart-lung machine. The first of these factors, the use of heparinized partly clotted blood in the heart-lung machine, might be expected to produce a "shift to the right" in the plasma coagulation components, namely, a decrease in plasma factors, particularly platelets and fibrinogen, and an increase in the active serum factors. The effect of the heart-lung machine on the blood coagulation factors has been considered in detail elsewhere[17] and may be summarized for the purpose of this discussion by indicating that it would contribute to the thrombocytopenia and fibrinogenopenia. Finally, the use of heparin and heparin antagonists tend to make

somewhat uncertain the relationship of the immediate postoperative sample to the preoperative samples, for certain of the coagulation tests, such as thromboplastin generation, prothrombin consumption, one-stage prothrombin, factor V, and factor VII. Inasmuch as both the group of bleeders and the group of nonbleeders undergoing open heart surgery were subjected to the same procedures, it seems permissible to compare the two with the reservations already noted. The platelet studies indicate that the bleeders' platelet levels exhibited a greater fall from the initial to postoperative period. However, of much significance is the fact that at the time hemorrhage was usually manifest (postoperative and 2-hour postoperative) the platelet level of bleeders had not undergone a greater fall than nonbleeders nor was it different in absolute value from the platelet level of nonbleeders. We therefore do not find evidence to support the concept that thrombocytopenia "causes," that is, is "necessary and sufficient" for the production of hemorrhage. We have been unable to confirm the impression of Krevans and Jackson[9] as to the etiologic role of thrombocytopenia. Considering this discrepancy it should be noted that the patients in Krevans and Jackson's group were undergoing different procedures, the platelet level was somewhat lower than observed in our group, bleeding manifested itself many hours later than in our group, and the extracorporeal apparatus with its attendant variables was not utilized. The question therefore arises as to whether we were studying the same syndrome. It is our working hypothesis that the bleeding syndrome was the same in both cases. It would have been helpful had previous studies been able to include a control group of patients receiving massive transfusion but not exhibiting hemorrhage. In this study it may be seen how valuable the control group has been. Examination of the bleeders undergoing open heart as well as closed heart surgery shows that the outstanding single finding is a relative thrombocytopenia. It would have been tempting to assign a causal role to this thrombocytopenia, particularly when it is noted that the level of platelets in both groups of bleeders correspond. However, consideration of the platelet level of the controls rationally leads to the conclusion that thrombocytopenia while possibly "necessary" was not "sufficient" to produce the hemorrhage. We have been forced therefore to regard the thrombocytopenia as a result of massive transfusion rather than a cause of the hemorrhagic syndrome. Experimental work in our laboratory[6, 17] on this point supports the clinical findings noted here.

The data presented reflect merely the quantitative evaluation of intact platelets. Klein and Djerassi[8] showed that during the course of the operation, an acute quantitative decrease in the number of circulating platelets is due in part to the rupture and liberation into the circulation of platelet contents including those platelet factors which have an effect on the plasma coagulation factors as well as possibly an effect on capillary integrity. The relationship then between acute change in number of intact platelets and its effect on the plasma coagulation factors as well as the vasculature is at present speculative.

We have considered the recalcified plasma clotting time to be a measure of integrated functioning of plasma coagulation factors. The following were

the outstanding alterations in plasma recalcified clotting time in comparing bleeders and nonbleeders undergoing open heart surgery. The bleeders had a prolonged plasma clotting time at the 2-hour postoperative and 24-hour postoperative period when compared with the initial values ($p = 0.01$). This was not true of the group of nonbleeders. It was also found that the changes observed in the values from the initial to the postoperative period are significantly greater for the group of bleeders as compared to the group of nonbleeders ($p < 0.05$). However, for any given time of analysis there is no significant difference between the values of the two groups. The positive differences between groups do not appear to be functionally significant regardless of statistical analysis. Thus evaluation of results of this test reveals no differences between bleeders and nonbleeders which we consider significant at this time.

An analysis of the *first stage* of coagulation, as measured by the thromboplastin generation test, indicates the following key findings when bleeders and nonbleeders are compared: there was no difference in absolute value at any given time of analysis between bleeders and nonbleeders, nor were the changes in bleeders' values greater than those of nonbleeders over any interval. In summary, we cannot definitely assign an etiologic role to deficiency in the first stage of blood coagulation in the production of the hemorrhagic diathesis. An examination of the prothrombin consumption values provides the same conclusion, namely, no significant difference for any given time of analysis and in general is consistent with the interpretation afforded by analysis of the thromboplastin generation test.

An analysis of the *second stage* of coagulation as reflected in one-stage prothrombin results indicates the following key findings when bleeders and nonbleeders on open heart surgery were compared: no statistical difference between the values of the group for any given period nor for changes of values between any given times. Thus, we are unable to assign an etiologic role in the production of the hemorrhagic diathesis to any of the factors concerned with the one-stage prothrombin time.

Analysis of the *third* and *final* stage of coagulation by measurement of fibrinogen levels indicates the following key points when bleeders and nonbleeders undergoing open heart surgery were compared: no statistically significant difference between the values for the two groups for any given time of analysis nor for changes in values between any two given times of analysis. Both groups showed a remarkable rebound at 24 hours. Fibrinogenopenia, therefore, does not play an important etiologic role in the production of the hemorrhagic diathesis.

Consideration of the data for fibrinolysin has indicated that sporadic lysin titers were found proportionally equal in both bleeders and nonbleeders. Moreover, among bleeders, only 2 patients manifested a significant fibrinolysin titer which could be correlated with decreased fibrinogen level. In summary, fibrinolysin does not seem to have played an important role in the production of the hemorrhagic diathesis seen in patients undergoing open heart

surgery. Thus, we have been unable to confirm the report of Cliffton and associates[4] who found a correlation among fibrinolysin, decreased fibrinogen, and oozing.

Thus, examination of the mean values of individual coagulation tests did not disclose any biologically significant differences in the platelets or plasma coagulation factors between the group of bleeders and nonbleeders undergoing open heart surgery.

Examination of the data for each individual bleeder and the interpretation of the same in a given case, however, has led to the following findings: 2 patients exhibited thrombocytopenia consistent with the observed hemorrhage and one patient exhibited an acute deficiency in thromboplastin generation which was corrected in vivo by the administration of Cohn fraction I. This correction manifested itself both clinically and in laboratory tests. One patient manifested a somewhat severe hypoprothrombinemia, two patients exhibited a high fibrinolysin titer, and one case showed no coagulation changes severe or striking enough to assign a deficiency. It is difficult to relate this varied picture to any simple mechanism in the production of hemorrhage. Zucker and associates[18] have found a somewhat similar picture in a group of 15 bleeders among 78 patients studied. They have noted a "correlation" between multiple defects and bleeding. The defects, however, do not seem to permit a definite statement of mechanism or to afford a general approach for practical management in the absence of detailed study of such cases. We note that the thrombocytopenia observed in their group of patients was manifested approximately at the same time as it was observed in our cases. There is some discrepancy in the incidence of fibrinolysin when the two studies are compared. This may be due to differences in methodology employed or to the fact that their cases included a high number of patients with neoplasms.

Data on patients undergoing closed heart and noncardiac surgery have unfortunately been limited to date. This limitation includes lack of sequential analysis and also lack of the controlled group: patients undergoing the same operative procedure receiving similar volumes of blood but not exhibiting the hemorrhagic manifestations. Results of analysis with this group indicate in general a thrombocytopenia and a marked fibrinogen rebound at 24 to 72 hours postoperative. It is quite remarkable that the values for the individual factors and coagulation tests corresponded very closely to those of bleeders undergoing open heart surgical procedures. Considering the differences between procedures and the number of variables operative, the interpretation of this coincidence is conjectural at present. Thrombocytopenia and other coagulation changes observed did not appear to be correlated with the volumes of blood received up to the time that hemorrhagic manifestations were first noted. This is true of the studies 2 hours postoperatively as well as the studies from 1 to 3 days postoperatively. It is also interesting that fibrinolysin results were not impressive in this group.

Detailed studies of the platelet and plasma coagulation factors of the 38 patients presented herein fail to indicate any significant differences between

bleeders and nonbleeders. There are, however, consistent findings of lower values or greater relative decreases in various coagulation factors for bleeders. We do not know if the summation of these individual nonsignificant differences is significant in the aggregate such that the bleeders' hemostatic mechanism is significantly more impaired than that of nonbleeders. It will be remembered that the results of the plasma recalcified time are suggestive of such a tendency, though we are not impressed with the differences on an absolute basis. This problem is being studied further and the role of the blood vasculature is being included in the study.

CONCLUSIONS

1. Thrombocytopenia was a finding common to bleeders and nonbleeders alike and was not sufficient to produce hemorrhage.

2. A fibrinogen drop and fibrinolysin titers were common to both groups and were not impressive.

3. A common cause for bleeding was not evident for all cases.

4. The defects exhibited by the bleeders embraced all phases of the blood coagulation mechanism.

5. Massive transfusion was not sufficient to produce the hemorrhagic manifestations observed.

6. Massive transfusion was probably entirely or in large part a result of bleeding rather than a cause of bleeding.

SUMMARY

Coagulation factors in 16 patients were studied and analyzed to explain the syndrome of abnormal bleeding following massive blood replacement. A control group of 22 patients who did not bleed and were similarly treated was also analyzed.

A reconsideration of the term "hemorrhage due to massive transfusion," and a generalized approach to the syndrome of "unexplained bleeding in the surgical patient" is presented.

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THE USE OF HEPARIN TO MINIMIZE THROMBOCYTOPENIA AND BLEEDING TENDENCY DURING HYPOTHERMIA

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INDUCED hypothermia as used clinically today is a safe procedure. The major problems of ventricular fibrillation and rewarming acidosis have been eliminated by proper body temperature control and by proper anesthetic techniques.[4, 10] The remaining problem in clinical hypothermia is an occasional bleeding tendency. The incidence of hemostatic difficulties is unknown but it has been sufficient to stimulate investigation in many centers where hypothermia is used as an anesthetic adjunct in cardiovascular surgery.[2, 3, 5, 8-11]

Comprehensive studies of the coagulation mechanism indicate that thrombocytopenia is probably the most important factor in hypothermic bleeding.[2, 3, 5, 8-11] Thrombocytopenia occurring with low body temperatures was described as early as 1938.[7] As recently reported by this laboratory[10] and previously by others,[3, 8, 9] the thrombocytopenia is temporary. The platelets fall as body temperature falls and return to normal upon rewarming. The fall is approximately proportional to the fall of body temperature in any one individual.

Ellis, Kleinsasser, and Speer[3] compared dogs subjected to cardiovascular surgery under hypothermia with and without the use of heparin. They found that 2 to 3 mg. of heparin per kilogram of body weight reduced the fall of platelets. Alterations of other factors they studied (proaccelerin, proconvertin, and prothrombin) were similarly minimized. They believed heparin decreased intravascular clotting which resulted from decreased cardiac output, increased viscosity of blood, and the release of tissue thromboplastin by lung trauma. No explanation of the return to normal levels of platelets during rewarming was offered.

Villalobos, Adelson, Riley, and Crosby[8, 9] followed dog platelets labeled with radiophosphorus and found that platelets were sequestered in the liver and spleen during hypothermia and that approximately 80 per cent returned to the circulation as rewarming occurred. They described no alteration of megakaryocytes.

This current study was stimulated by the observation that our neurosurgical associates who use extremely small amounts of heparin with precooling vessel cannulations seldom encounter hemorrhagic difficulties. By recalling the study of Ellis and associates,[3] an experiment was devised. During hypothermia, serial platelet counts were compared with and without the influence of heparin both

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experimentally[3] and clinically. To our knowledge the influence of heparin on hypothermic thrombocytopenia in clinical patients has not been described previously.

METHOD

Experimental Animals.—Mongrel dogs weighing 5 to 8.5 Kg. were used. All had normal erythrocyte sedimentation rates. All were fasting. Most were mature. All received 0.01 grain of atropine sulfate and 50 mg. of Demerol prior to induction which was carried out with thiopentone sodium. The dogs were curarized, intubated, and hyperventilated with intermittent positive pressure oxygen at a rate of 24 respiratory excursions per minute. The left external jugular vein was cannulated with a clean siliconized polyethylene tube which was kept clear by a slow saline drip. Prior to induction blood samples were taken from a limb vein. All subsequent samples were taken from the cannulated external jugular vein.

The first group served as a control to establish the influence of the anesthetic technique on platelet counts. Four animals were anesthetized and periodic platelet counts were done.

All other animals underwent hypothermia. Cooling was carried out in an ice water bath at 4° C. Rewarming was by water immersion in a bath of 40° to 42° C. Rectal temperatures were used as the index of body temperature. Esophageal temperatures were used for verification and to estimate drift. An attempt was made to attain a uniform minimum rectal temperature of 24° to 26° C.

Blood samples for platelet counts were taken prior to induction, at 35° C., and at 5 degree intervals thereafter, both on cooling and rewarming. A sample was also taken at the lowest temperature reached. The first 2 c.c. of blood drawn from the polyethylene catheter were discarded. A 2 ml. sample was then drawn into a sterile syringe and quickly transferred with a minimum of trauma to a siliconized graduated glass tube containing 0.2 c.c. of citrate solution. All platelet counts were performed by the same technician promptly after the blood was drawn. Counts were done by a direct technique using a modification of the Rees-Ecker method utilizing brilliant cresyl blue diluting fluid.

The second group of 6 dogs underwent hypothermia as described. The effect of low body temperatures on the platelet counts was thereby demonstrated.

The third group of 6 dogs also underwent hypothermia but prior to induction were given 0.5 to 1.0 mg. of heparin per kilogram of body weight. The modifying influence of heparin on hypothermic thrombocytopenia was illustrated.

Clinical Investigation.—The patients investigated were consecutive adult cases undergoing hypothermia for open heart surgery, chiefly the repair of atrial septal defects. The anesthetic technique has been previously described.[4, 10] Blood samples were taken from either the external jugular vein or the femoral vein. As in the experimental group, platelet counts were taken prior to induction, at 35° C., and at 5 degree intervals thereafter on cooling and rewarming. The minimum rectal temperatures were 29° to 31° C.

The first group of 6 patients received no heparin prior to induction. The second group of 6 patients received 15 to 20 mg. of heparin intravenously prior to induction. Generally, small patients, 45 Kg. or less, received 15 mg. of heparin while larger patients such as those over 50 Kg. received 20 mg. of heparin.

RESULTS

Experimental Group.—

1. In dogs subjected to an anesthetic alone, there was no alteration in platelet levels.

2. In the hypothermic anesthetized dogs, the fall of platelets averaged 63 per cent of the normal count. The greatest fall occurred at the lowest temperatures reached (Fig. 1).

3. In the dogs which were cooled, anesthetized, and given heparin in the doses specified, the fall of platelets averaged 41 per cent of the normal count (Fig. 2). No hemorrhage was noted in either the heparinized or the non-heparinized group.

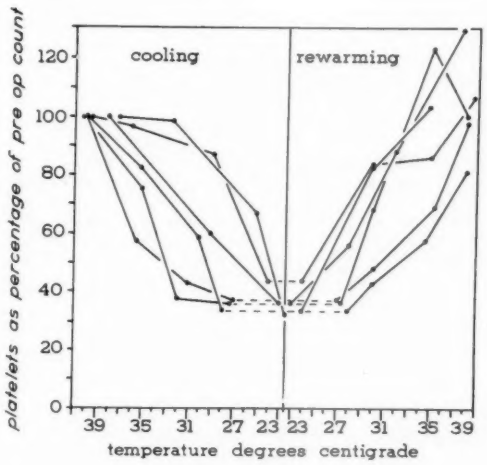


Fig. 1.

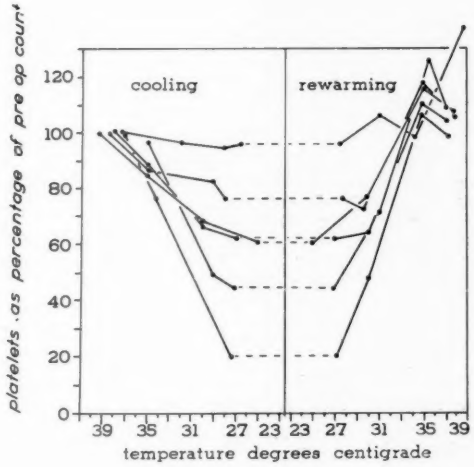


Fig. 2.

Fig. 1.—Serial platelet counts in dogs (control group) expressed as a percentage of preoperative count illustrating a consistent fall which averaged 63 per cent. Rectal temperatures at a minimum of 24° to 26° C.

Fig. 2.—Serial platelet counts in dogs (experimental group using heparin) illustrating hypothermic thrombocytopenia modified by heparin. Average fall of platelets was 41 per cent as compared to 63 per cent in the group receiving no heparin (Fig. 1).

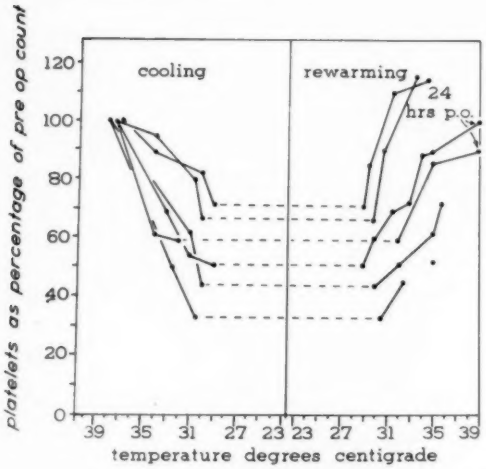
Clinical Cases.—

1. In 6 consecutive clinical cases which underwent hypothermia and received no heparin prior to induction, the platelet fall averaged 46 per cent (Fig. 3). One of these cases demonstrated a marked hemorrhagic tendency which was controlled. This was the patient with the lowest platelet count.

2. The 6 patients who received small doses of heparin prior to induction and who underwent subsequent hypothermia had an average platelet fall of only 19 per cent. This difference is statistically significant (Fig. 4). No hemorrhagic tendencies were noted in this group.

Prior to the use of small doses of heparin routinely in hypothermia, hemorrhagic tendencies were noted in 3 of 14 cases. One of these patients died within 12 hours of operation. At autopsy a large mediastinal hematoma and hemothorax were found.

In 10 consecutive cases in which small doses of heparin were used to modify the hypothermic thrombocytopenia, there was no hemorrhagic tendency or uncontrollable oozing.



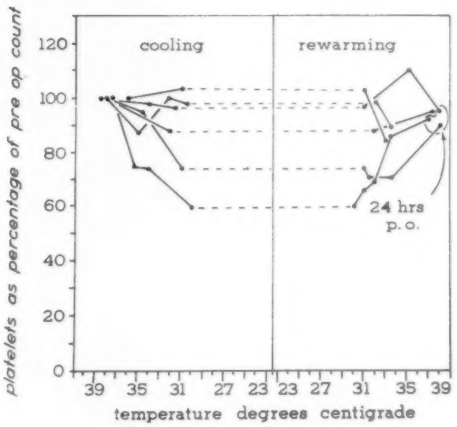


Fig. 3.—Serial platelet counts in clinical cases of open heart surgery (control group) expressed as a percentage of preoperative count illustrating a consistent fall which averaged 46 per cent. Rectal temperatures at a minimum of 29° to 31° C.

Fig. 4.—Serial platelet counts in clinical open heart surgical cases (using small doses of intravenous heparin) illustrating hypothermic thrombocytopenia modified by heparin. Average fall of platelets was 19 per cent as compared to 46 per cent in the group which received no heparin prior to induction (Fig. 3).

DISCUSSION

The doses of heparin used in this experiment were somewhat smaller than reported previously.[3] This was an attempt to keep clotting times normal or near normal. Preliminary experiments on dogs indicated that less than 0.5 mg. per kilogram did little to influence the thrombocytopenia of hypothermia. Doses in the range of 0.5 to 1.0 mg. per kilogram appeared to be equally effective in reducing the thrombocytopenia. Larger doses prolonged clotting times excessively and were no more efficient in preventing thrombocytopenia than the small doses.

The dose chosen for clinical use, about 0.33 mg. per kilogram, differed from that used experimentally because there is a difference in the physiochemical properties of dog and human platelets. The average length of dog platelets is about twice that of human platelets. Dog platelets comprise 1.04 per cent of the blood volume while human platelets comprise only 0.49 per cent of the blood volume.[7] In addition, dog platelets agglutinate more readily than human platelets. Possibly, this factor might explain the better results achieved clinically with heparin than those found experimentally.

It is our impression that heparin minimizes thrombocytopenia only if given just prior to cooling. It will not increase the number of circulating platelets in a patient already hypothermic.

Clinical patients received an average of 3 units of heparinized fresh blood collected in siliconized bottles; each unit contained 18 mg. of heparin. The heparinized blood was not usually started until the minimal temperatures were approached and well after surgery commenced. When rising rectal temperatures indicated rewarming and after the definitive surgery was performed, protamine sulfate sufficient to cover the heparin was given. This was usually in divided doses about one-half to three-quarters of an hour apart and covered the heparin given prior to induction and also the heparin in the transfusions.

The manner in which heparin minimizes thrombocytopenia in hypothermia can only be postulated. Assuming that thrombocytopenia is due to sequestration as indicated by Villalobos,[8, 9] presumably heparin acts by reducing the adhesiveness or agglutinability of platelets below a critical level.[1]

This report concerns the lessening or prevention of thrombocytopenia during hypothermia by the somewhat paradoxical use of heparin. It is the clinical impression of those associated most closely with hypothermia in this center that some cases show an abnormal bleeding tendency during hypothermia. This has been minimized since heparin has been used routinely. No hemorrhagic complications have occurred. However, this is a very small series. Thrombocytopenia cannot be regarded as the cause of all hemorrhage occurring under hypothermia. Any procedure involving large blood transfusions may lead to coagulation problems.[6, 12] In most surgical hemostatic problems, and especially those in cardiovascular surgery, there are usually several defects in the coagulation mechanism which probably in combination cause bleeding.

In continuance with the study of hypothermic bleeding, this laboratory presently is attempting to isolate and store human platelets that would be readily available should emergencies arise.

SUMMARY

1. It is our experience that in open heart surgery with hypothermia an occasional patient demonstrates an abnormal bleeding tendency.

2. This study would suggest that thrombocytopenia is the major factor in hypothermic bleeding.

3. Thrombocytopenia during hypothermia can be minimized experimentally by the use of small doses of heparin given intravenously prior to cooling.

4. In the small series of clinical cases reported the use of heparin has minimized thrombocytopenia and has eliminated bleeding tendencies.

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EFFECT OF CHLORPROMAZINE ON RENAL FUNCTION AND HEMODYNAMICS PARTICULARLY DURING HEMORRHAGIC HYPOTENSION

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INTRODUCTION

THE aim of therapy in shock due to hemorrhage has been early restoration of blood volume with return of the blood pressure to normal levels. Blood pressure and pulse have been the prime clinical indices of adequate therapy. Irreversibility of shock after inadequate or tardy therapy is manifested by a recurrent hypotension followed by death, in spite of further blood replacement. Further maintenance of blood pressure under these circumstances has been attempted, using vasopressor agents such as Levophed. The use of Levophed has been mainly on empirical grounds. Some recent experimental work has shown that the use of Levophed may actually be detrimental in certain situations of hemorrhagic shock.[4]

Stimulated by reports from the French literature that certain sympatholytic agents seem to improve survival after shock, many laboratories have investigated the effects of various adrenolytics administered before and after the induction of traumatic and hemorrhagic shock. In general, the results have been that pretreatment with chlorpromazine or dibenamine yields an increased survival in dogs or rodents subjected to various types of shocking procedures. The usual experiment consists of administration of about 2.5 to 5.0 mg. per kilogram of chlorpromazine to the experimental group, followed either by hemorrhage to a given level or a standardized trauma both to control and experimental groups. Survival of the experimental group has usually been found to be longer than that of the controls. When the same method of approach is attempted after the induction of shock, using similar dosages of chlorpromazine or dibenamine, there has been no beneficial effect; in fact, the survival rate has usually been lower in the treated groups.

Using a much smaller dose of dibenamine, H. C. Wiggers and associates[14] reported 90 per cent survival after a hemorrhagic shocking procedure, when treatment was given after the inception of shock compared to 30 per cent survival in control dogs.

The renal blood flow in shock, following the administration of dibenamine, was studied by Brandfonbrener and Geller[3] who found that dibenamine (3 to 6 mg. per kilogram) given during a period of hypotension at 50 mm. Hg caused a definite increase of renal blood flow. In their small groups, they saw no improvement in survival following treatment.

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More recently, a report by Inglis and associates[8] has indicated that survival time of dogs could be prolonged following hemorrhagic hypotension by using small intravenous doses of chlorpromazine. This group gave chlorpromazine in 2 mg. doses every 15 minutes to dogs maintained at an arterial blood pressure of 30 mm. Hg. Direct portal vein blood flow measurements in these animals revealed a significant elevation of mesenteric blood flow in the chlorpromazine-treated group during hemorrhagic shock.

Savlov and Regelson[9] demonstrated diuresis during extremely low levels of blood pressure after hemorrhage in dogs treated with small doses of chlorpromazine (0.2 mg. per kilogram). The nature of this diuresis was not clear. They noted that, while animals treated with this dosage of chlorpromazine usually survived their technique of hemorrhage (technique of Wiggers), larger doses usually caused almost immediate drop in blood pressure and death.

Because the nature of the diuresis following chlorpromazine in hemorrhagic hypotension was not well understood, it was felt that studies of renal hemodynamics and tubular reabsorption might cast some light upon the mechanism of action of chlorpromazine on the peripherally vasoconstricted, shocked animal.

METHODS AND MATERIALS

Mongrel dogs, weighing between 15 and 23 kg., were anesthetized with sodium pentobarbital (30 mg. per kilogram). Urine was collected from the bladder by an indwelling Foley catheter. Arterial blood pressure was measured by a Statham strain gauge connected to a polyethylene catheter placed in a femoral artery and threaded at least 3 inches cephalad. Continuous record of blood pressure was then made with a multichannel recorder. Priming hydration of dogs consisted of 20 to 30 ml. of 5 per cent dextrose or isotonic saline per kilogram of body weight. To this was added 4 or 8 per cent urea when osmotic diuresis was desired.

Direct measurements of renal blood flow were made after the method of Selkurt,[11] by passing a polyethylene cannula with an inside diameter of 0.106 inch into the left renal vein from the right jugular vein and ligating it in place via an abdominal incision. Blood flow was maintained into the opposite jugular vein through a T-tube connection which was opened with synchronous occlusion of the distal limb for 30-second blood collections from the renal vein into a graduated cylinder.

Inulin and para-aminohippurate (PAH) clearances were done according to the methods described by Smith.[13]

Experimental Procedures.—

Group I. Effect of chlorpromazine on tubular reabsorption of water (6 dogs):

A. Three hydrated dogs in water diuresis were given a continuous intravenous infusion of pitressin, 100 milliunits per hour. During maximal antidiuresis, chlorpromazine (1 mg. per kilogram) was given intravenously.

B. A 13.7 Kg. dog in water diuresis was gently bled of 50 ml. of blood through a previously placed vein cannula. Urine volumes and osmolarities were

recorded. Water diuresis was established again and chlorpromazine (0.2 mg. per kilogram) was given intravenously at the same time that 50 ml. of blood was withdrawn.

C. Two dogs were rapidly infused with 10 to 12 ml. per minute of 4 per cent urea in 5 per cent dextrose solution. When urinary output was established at a steady rate of over 15 ml. per minute, chlorpromazine (0.2 mg. per kilogram) was given intravenously.

Group II. Effect of chlorpromazine on urinary flow in the presence of acute protein dilution (2 dogs):

After hydration and maintenance of flow at 3 ml. per minute with a balanced electrolyte solution* containing 4 per cent urea, the dogs were hemorrhaged to a blood pressure level of 50 mm. Hg and maintained for 3 hours at the level by intermittent withdrawal of blood as needed. One dog was given chlorpromazine (0.2 mg. per kilogram) intravenously after 30 minutes of hypotension.

Group III. Effect of chlorpromazine on renal blood flow: (A) during hemorrhagic hypotension (2 dogs) and (B) at normal blood pressure:

A. Direct measurements of renal blood flow were made as follows: (1) at normotensive levels, (2) following hemorrhage to 60 mm. Hg, and (3) following administration of chlorpromazine (0.2 mg. per kilogram) to the hypotensive animal.

B. Inulin and PAH clearances were done before and after administration of chlorpromazine (0.2 mg. per kilogram) in unilaterally nephrectomized dogs.

Group IV. The combined use of Levophed and chlorpromazine in hemorrhagic hypotension (2 dogs): Inulin and PAH clearances were done after one hour of equilibration in hydrated dogs maintained in diuresis with 4 per cent urea in saline infusion. Clearance periods of 15 to 30 minutes were as follows: C_1 and C_2 at normotensive levels, C_3 and C_4 at blood pressure of 60 to 80 mm. Hg after acute hemorrhage, C_5 and C_6 after administration of chlorpromazine (0.2 mg. per kilogram) and simultaneous maintenance of blood pressure at 90 to 100 mm. Hg with Levophed infusion, C_7 and C_8 following cessation of Levophed drip, with addition of small doses of chlorpromazine to hold blood pressure below 80 mm. Hg.

Group V. Effect of chlorpromazine on vascularity of the shocked rat kidney: Observations were made on the kidneys of etherized white rats, 400 to 500 Gm. in weight, after intra-aortic injection of Vasoflavine 10 per cent (method of Schlegel[10]) for demonstration of renal vascularization under ultraviolet light.

The rats were grouped as follows: (I) normotensive (4 rats), (II) hemorrhage to blood pressure of 60 mm. Hg (5 rats), and (III) hemorrhage to blood pressure of 60 mm. Hg followed by injection into aorta of chlorpromazine (0.2 mg. per kilogram) (6 rats).

*Balanced electrolyte solution: 912.5 ml. isotonic saline, 2.5 ml. KCl solution containing 5 mEq. potassium, 30 ml. $NaHCO_3$ solution containing 46 mEq. sodium, and 80 ml. of 50 per cent urea.

RESULTS

I. Effect of Chlorpromazine on Tubular Reabsorption of Water.—As shown in the accompanying chart (Fig. 1), the administration of chlorpromazine to a dog in maximal antidiuresis had little or no tendency to increase urine volume or to decrease tubular reabsorption of water.

It was noted, in this dog as well as in several other experimental animals in which similar procedures were carried out, that before and after the administration of chlorpromazine there was no significant change in urine osmolarity after the administration of the drug. Blood pressures were the same or slightly lower after the administration of chlorpromazine.

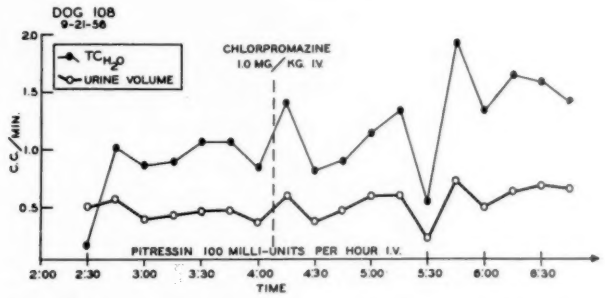

Fig. 1.—Administration of chlorpromazine (1.0 mg. per kilogram) to a normotensive dog in maximal antidiuresis from exogenous pitressin, 100 milli-units per hour. There is no increase in urine volume nor decrease in $T^c_{H_2O}$.

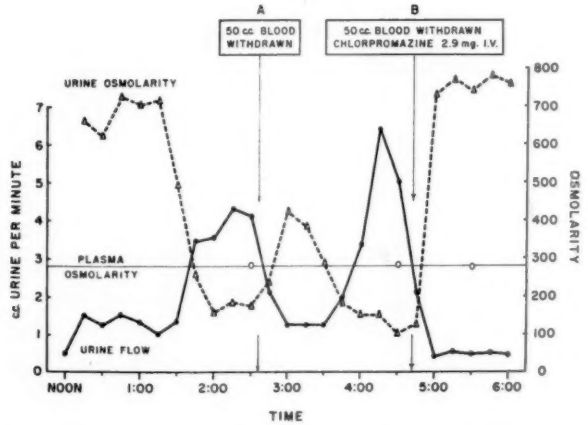

Fig. 2.—Failure of chlorpromazine to inhibit the antidiuresis following withdrawal of blood.

As shown in Fig. 2, the withdrawal of 50 ml. of blood caused an immediate antidiuretic effect with a drop in urine volume and a rise in urine osmolarity to levels above that of the plasma. When chlorpromazine was given simultaneously with the withdrawal of the blood, there was no diminution of the antidiuretic effect. In fact, it seems actually to have been increased, although this is not necessarily the effect of chlorpromazine.

II. Effect of Chlorpromazine on Urinary Flow in the Presence of Acute Protein Dilution.—Urine flow ceased almost immediately as the blood pressure approached 60 mm. Hg in both animals. Animal No. 1 remained anuric during the entire period of hypotension. There was no urine flow above 0.48 ml. per

minute for a period of 3 hours during which the serum protein dropped to 2.1 Gm. per cent and the hematocrit to 13 per cent. The second animal likewise became anuric at the hypotensive levels. The serum protein was 2.92 Gm. per cent and the hematocrit 25 per cent. After the blood pressure had been approximately 50 mm. Hg for 30 minutes and when the hematocrit was 29 per cent and the serum protein 3 Gm. per cent, 2.4 mg. chlorpromazine was given intravenously (0.2 mg. per kilogram). Following this the blood pressure dropped to 30 but gradually returned to approximately 45 for the remainder of the experiment. Forty minutes after administration of chlorpromazine, hematocrit was 25 per cent and the total protein was 3 Gm. per cent. Ninety minutes after administration of chlorpromazine, hematocrit was 25 per cent and the serum protein 2.92 Gm. per cent. In the 105 minutes following the administration of chlorpromazine, with blood pressure levels at 50 or below, there was a total urinary output of 71.5 ml. The rate varied at different times during this period, rising as high as 1.5 ml. per minute. At the end of the experiment, after 105 minutes of acute hypotension, the hematocrit was 25.3 per cent and total serum protein 2.92 Gm. per cent.

The urine excreted during this period was hyperosmolar to serum with a urinary osmolarity of about 725. Urine sodium was 52.9 mEq. per liter, potassium was 21.6 mEq. per liter, and chloride 46.9 mEq. per liter.

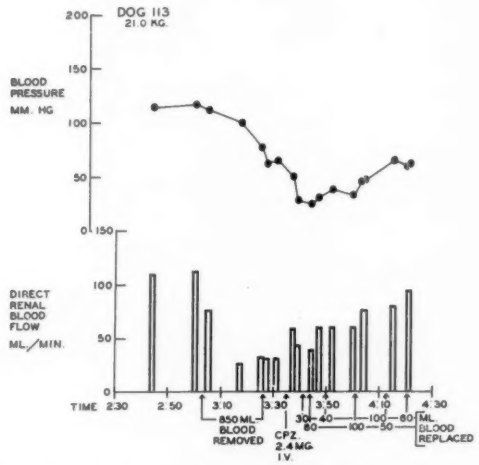

Fig. 3.—Effect of chlorpromazine on direct renal blood flow during hemorrhagic hypotension in the dog. Renal blood flow increases although blood pressure falls.

Summary: Acute serum dilution alone at low hematocrit and hypotensive levels does not induce diuresis. Under similar conditions, administration of chlorpromazine does induce diuresis.

This experiment was carried out for the obvious purpose of ruling out protein dilution alone as a possible mechanism of diuresis at hypotensive levels.

III. Effect of Chlorpromazine on Renal Blood Flow (A) During Hemorrhagic Hypotension and (B) in Normotensive Dogs.—

A. Fig. 3 illustrates the direct renal blood flow measurements in Dog 113, representative of both experiments. At 60 mm. Hg blood pressure, there was

approximately 32 ml. per minute renal flow. After administration of chlorpromazine (0.2 mg. per kilogram), blood pressure dropped to a level of about 30 mm. Hg but the renal blood flow rose to well over 40 ml. per minute. When blood was reinfused to maintain the blood pressure at 60 mm. Hg, the renal blood flow was 80 to 90 ml. per minute.

Summary: Following administration of chlorpromazine (0.2 mgm./kg.) to a dog in hemorrhagic hypotension, renal blood flow by direct measurement rose significantly.

B. Table I gives inulin and PAH clearances in 2 anesthetized dogs before and after intravenous administration of chlorpromazine slowly over a 3-minute period so that effect on blood pressure was minimal.

TABLE I

	DOG 163		DOG 2	
	CLEARANCE 1	CLEARANCE 2	CLEARANCE 1	CLEARANCE 2
Before chlorpromazine				
Blood pressure (systolic)	165	165	180	180
Inulin clearance (ml./min.)	35	41	69	50
PAH clearance (ml./min.)	156	172	127	155
After chlorpromazine				
Blood pressure (systolic)	165	170	165	150
Inulin clearance (ml./min.)	45	43	57	45
PAH clearance (ml./min.)	180	179	162	140

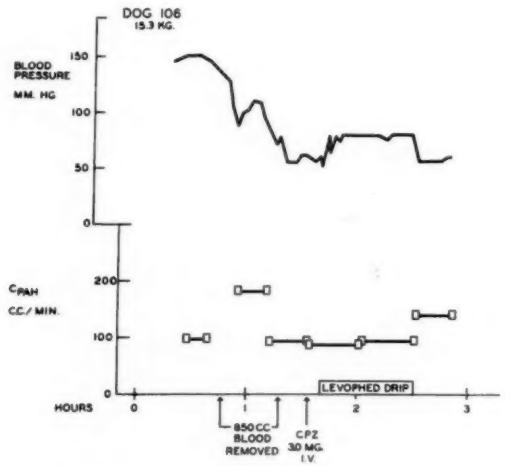

Fig. 4.—Failure of renal blood flow to increase at 80 mm. Hg following combined use of chlorpromazine and Levophed.

IV. The Combined Use of Levophed and Chlorpromazine in Hemorrhagic Shock (2 Dogs).—

Tables II and III give the volume and clearances of inulin and PAH during the experimental periods. Fig. 4 illustrates the renal blood flow and its relationship to blood pressure during the course of one experiment. It is seen that an initial transient rise in PAH clearance was seen during the time when bleeding was being carried out before the blood pressure had gone below 100 mm. Hg.

There was no significant difference between the clearances at the 60 mm. Hg before the administration of the drugs and after the drugs were started. However, after the Levophed drip was terminated, even though there was an abrupt drop in blood pressure to 60 or below, there was moderate increase in the renal blood flow as measured by the PAH clearance. This did not appear in the second dog.

TABLE II

	NORMOTENSIVE		AFTER HEMORRHAGE		AFTER CHLORPROMAZINE WITH LEVOPHED		NO LEVOPHED, CHLORPROMAZINE ADDED	
	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
Blood pressure (mm. Hg)	150	–	90-112	60-70	80	80	56-60	–
Volume (ml./min.)	4.9	–	4.8	1.4	1.6	2.5	0.7	–
Inulin clearance (ml./min.)	31	–	66	22	26	21	15	–
PAH (clearance (ml./min.	98	–	188	94	91	93	141	–

TABLE III

	NORMOTENSIVE		AFTER HEMORRHAGE		AFTER CHLORPROMAZINE WITH LEVOPHED		NO LEVOPHED, CHLORPROMAZINE ADDED	
	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
Blood pressure (mm. Hg)	185	185	80-100	80-110	75-90	75-88	75-85	77-85
Volume (ml./min.)	3.9	4.5	0.81	0.74	0.95	0.42	0.42	0.64
Inulin clearance (ml./min.)	56	77	52	56	79	36	33	44
PAH clearance (ml./min.)	256	268	258	205	200	163	212	197

Discussion: Administration of Levophed in dosage sufficient to elevate the blood pressure during hemorrhagic hypotension in the face of preliminary administration of chlorpromazine maintains the peripheral vasoconstriction. After cessation of the Levophed the chlorpromazine may exert its vasodilating effect with subsequent rise in the renal blood flow. A possible usefulness of the two drugs combined for treatment in shock was sought, but, on evidence presented here, it would not seem that the combined therapy would be advantageous.

V. Effect of Chlorpromazine on the Vascularity of the Shocked Rat Kidney.—Fig. 5 is an example of a rat kidney at normal blood pressures 60 seconds after the intra-aortic injection of Vasoflavine 10 per cent. All glomeruli and vessels are apparent, without areas of ischemia.

Fig. 6 is an example of rat kidney subjected to hypotension of 60 mm. Hg without further treatment. Almost no dye is apparent in the blood vessels of glomeruli 60 seconds after injection.

Fig. 7 is an example of the right kidney of a rat subjected to hypotension of 60 mm. Hg and then treated with chlorpromazine (0.2 mg. per kilogram). There is an increase in the number of glomeruli visible, as compared with the

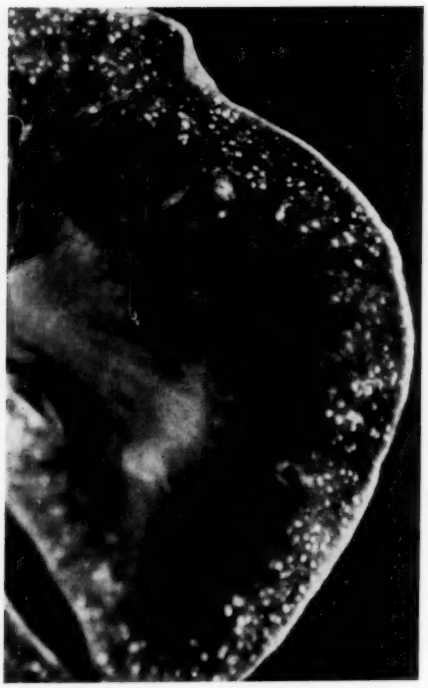

Fig. 5.

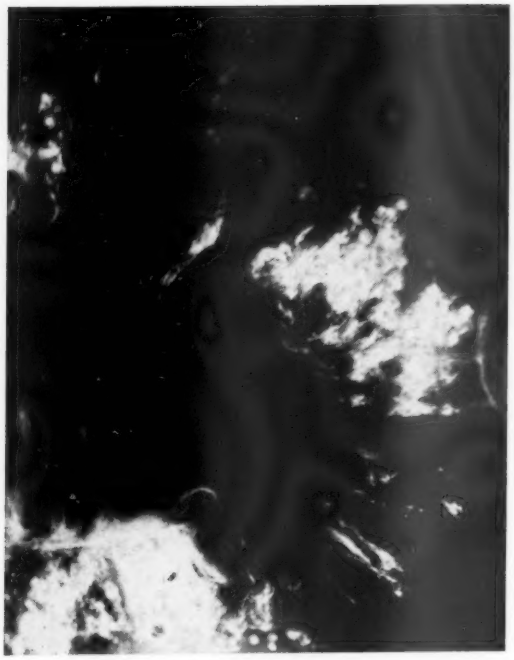

Fig. 6.

Fig. 5.—Photograph under ultraviolet light of normotensive rat kidney. Glomerular filling is apparent.

Fig. 6.—Hypotensive rat kidney without treatment. Rare glomeruli are seen. Great patches of cortical and medullary ischemia are apparent.

Fig. 7.—Hypotensive rat kidney treated with chlorpromazine. The medulla is highly perfused. A few glomeruli can be made out and more are present in the areas which are overexposed because of high concentration of dye.

purely hypotensive group. Medullary vessels are more prominent. The increase in medullary vasculature has been a constant finding. This correlates with the observed increase in PAH clearance in hypotensive animals following chlorpromazine, with associated decrease in the filtration fraction.

DISCUSSION

The diuresis in hemorrhagic hypotension seen following administration of chlorpromazine is most likely due to the increased perfusion of the organ, as demonstrated in the foregoing experiments. In all likelihood, this is secondary to the adrenergic blocking ability of chlorpromazine.

In no way do these results imply that the mechanism of protection in hemorrhagic shock by chlorpromazine is the same adrenergic blocking effect. While it is conceivable that the adrenolytic action of chlorpromazine produces protection in shock, certainly other possible mechanisms must be explored. Chlorpromazine has multiple actions, some of which appear to depend on an antiserotonin effect.[1] In addition, recent studies have shown that other adrenergic blocking agents protect in shock by virtue of direct biochemical linkages with sulfhydryl radicals[12] and possibly with other metabolic by-products of hypoxia.[15] Further exploration of these activities on the part of chlorpromazine is needed.

That a sympathetic blocking agent may be useful in the treatment of shock has recently been shown clinically, when several patients in profound hypotension were treated with Arfonad, a thiophanium derivative which blocks the sympathetic ganglia without the more peripheral adrenolytic properties of chlorpromazine.[5] We have measured renal blood flow in one dog utilizing direct blood flow measurements with Arfonad. The result has been much different from our results with chlorpromazine. Administration of Arfonad to a dog with a blood pressure of 60 mm. Hg following hemorrhage resulted in a slight drop in blood pressure and a decrease in renal blood flow of a significant degree.

Other possible mechanisms of action of chlorpromazine in shock than its adrenergic blocking effect and its possible capability of reacting chemically with the metabolic by-products of tissue hypoxia might be effects upon blood viscosity. Changes in the surface properties of erythrocytes during illness have been demonstrated by a number of investigators, particularly in traumatic shock.[2, 6, 7] These surface property changes result in erythrocyte clumping which, combined with vasoconstriction, increases the sluggishness of flow in the microcirculation. Prevention of clumping by a drug has not been demonstrated to date, although low molecular dextran infusions will temporarily offset red cell aggregation due to trauma and high viscosity infusions.[6] It would seem more likely that chlorpromazine would act to maintain microcirculatory flow by maintaining patency of the precapillary sphincters rather than by prevention of aggregation. Direct observations of the microcirculation in shock, before and after the administration of chlorpromazine, have not been carried out, to my knowledge.

The use of chlorpromazine in shock therapy has not been accepted widely, primarily because experimental studies of postshock treatment have not demonstrated improvement in survival. However, it may be inferred from the present

study that doses of a smaller order than those usually employed experimentally will increase perfusion of the kidney without significant lowering of the blood pressure. In situations of prolonged hypotension, where volume replacement is delayed or ineffective in restoring urine flow, renal ischemia may be inhibited by judicious use of chlorpromazine. If further depression of blood pressure occurs, Levophed may be used for maintenance, although Levophed in sufficient quantity to raise the blood pressure will abolish the effect of chlorpromazine.

Further survival studies as well as blood flow measurements in other vital organs (heart, liver, and brain) are needed to establish the eventual role of the adrenolytic drugs in the treatment of shock. The arteriosclerotic or otherwise borderline kidney is particularly susceptible to ischemia and might be protected from irreversible damage by a small increment in perfusion such as adrenergic blockade might afford. Such an effect might be demonstrated in a suitably prepared experiment, using animals in which renal function is marginal.

SUMMARY

1. The mechanism of diuresis following chlorpromazine in hemorrhagic hypotension was investigated in the dog. No effect of chlorpromazine on tubular reabsorption of water could be demonstrated.

2. Administration of small doses of chlorpromazine to dogs bled to blood pressures below 60 mm. Hg resulted in increased renal blood flow.

3. The increased vascularization of the kidney in shock following chlorpromazine was confirmed in rats, using the fluorescent dye Vasoflavine. While glomerular perfusion was increased to some degree, the circulation in the medullary portion of the kidney was improved more significantly.

4. Alleviation of renal ischemia in situations of profound vasoconstriction may be achieved by use of small doses of chlorpromazine.

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URINARY DIVERSION WITH BLADDER SUBSTITUTION

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WITH the advent of radical pelvic surgery for advanced cancer there is a growing interest in urinary diversion because such surgery entails, among other things, excision of the urinary bladder and transection of ureters at varying levels proximal to their entrance into the bladder. It would seem that no one surgeon has had sufficient personal experience with a wide variety of procedures to formulate judgment as to the preferred method for urinary diversion where some type of "artificial bladder" is constructed. At present, increasing experience is being accumulated with various procedures.

The two methods of relatively rapid and simple urinary diversion, aside from the question of bladder substitution, include cutaneous ureterostomy and ureterocolic anastomosis utilizing the intact colon.

A disadvantage of cutaneous ureterostomies is the relative difficulty in care in some instances because of frequent eventual stenosis of the orifices. Such patients must always be seen at regularly frequent intervals. Often catheters must be worn continuously and changed frequently by the physician in charge. When the bladder and lower colon are also absent there are 3 ostomies to care for. Pyelitis and calculi are not uncommon. Late ureteral fistulas may also be a complication, especially if there has been extensive radiation as the initial therapy for the pelvic cancer.

The disadvantages of ureteral implantation into the intact pelvic colon include: possible stenosis with ureteral obstruction, calculi formation, electrolyte imbalance (hyperchloremic acidosis), ascending infection, and difficult adjustment of the patient to urine excretion into the colon.

In the absence of complications, both of the afore-mentioned methods of urinary diversion may prove satisfactory and quite manageable; in such instances there is no problem of bladder substitution.

The present article is concerned not simply with urinary diversion but with urinary diversion *plus* bladder substitution. The purpose of this report is to review the several methods of urinary diversion and bladder substitution *now* practiced by surgeons interested in and carrying out, with some degree of consistency, radical excisional pelvic surgery for cancer and which methods have been *tested* by a certain measure of recent experience and have been reported as practical.

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At this point the reader's attention is drawn to the complete and exhaustive review published by Hinman and Weyrauch[11] in 1937 in which the accumulated literature since the earliest attempts in the mid-nineteenth century is discussed. This review was published just before the advent of modern radical pelvic surgery. All historical references in this report are drawn from Hinman and Weyrauchs' reviews. It is of interest that almost all conceivable possibilities for urinary diversion have been tried experimentally and/or clinically in the past. Most of the situations concerned the management of extrophy of the urinary bladder although diversion in the presence of pelvic cancer, especially cancer of the bladder also was not infrequently considered. It is of interest to recall that the first attempt at ureterocolic implantation in the human was recorded by T. Smith in 1879. The patient was a boy with extrophy of the bladder, and, extra-peritoneally through a lateral incision, the left ureter was transected, an opening was made in the sigmoid, and the ureter was "dunked" into the bowel. After a temporary fistula the wound healed. Many months later a similar procedure was carried out on the right side, and metallic suture material was used at the implantation site. Death ensued in a few days from infection, and necropsy revealed that the left kidney had been destroyed as a result of ureteral occlusion that had occurred some time previously (Fig. 1).

BLADDER SUBSTITUTION BY USING ILEOCECAL REGION

This procedure was initially conceived by Verhoogen in 1908. The cecum and terminal portion of ileum were isolated and continuity was re-established by ileocolostomy (ascending colon). The ureters were implanted into the cecum and the appendix was utilized for a conduit to the exterior. Two patients with carcinoma of the bladder were operated upon and both terminated fatally. In 1910, Makkas of Athens carried out the same procedure for extrophy of the bladder, staged the operation, and performed an ileocolostomy with the transverse colon instead of ascending colon, thus affording the use of the ascending colon together with cecum for the urinary reservoir.

In 1950 Bricker and Eiseman[4] reported 2 cases operated upon according to the above principles, but, shortly afterward, Bricker adopted another method (see below).

Gilchrist more consistently has utilized the isolated ileocecum and ascending colon for the urinary reservoir, implanted the ureters into the ascending colon, and employed the contiguous lowest segment of ileum for conduit to the exterior (Fig. 2). Under these conditions the ileocecal valve affords continence and the patient empties the reservoir by self-catheterization at intervals. Up to 1957, 53 patients received this procedure. Five patients at this time were beginning their fifth year. A recent evaluation of the method has been reported by Merricks and Gilchrist.[16]

BLADDER SUBSTITUTION BY USING SEGMENT OF SMALL BOWEL

It would appear the Cuneo was the first to utilize a segment of small bowel for urinary reservoir and conduct. He employed a loop of ileum 18 to 20 cm. long and isolated about 20 cm. above the ileocecal valve. The continuity of the

intestine was re-established by end-to-end anastomosis. The distal end of the isolated segment was brought downward and within the anal sphincter anteriorly to the anal canal after fashioning a plane by freeing up the mucosa of the anterior portion of the anal canal. The open end of the ileal segment was sutured

AN ACCOUNT OF

AN UNSUCCESSFUL ATTEMPT TO TREAT EXTROVERSION OF THE BLADDER BY A NEW OPERATION.

BY

THOMAS SMITH.

In devising means for the relief of this wretched deformity, attention has chiefly been directed to the most pressing of the evils attendant on the condition, namely, the absolute incontinence of urine; and since in these cases there is neither a receptacle for urine nor a retaining apparatus, surgical ingenuity has exercised itself chiefly in one of two directions: either in the formation of a receptacle for urine by plastic operations, or in attempts to divert the stream of urine into the lower bowel, so as to use the rectum as a common cloaca.

The plastic method, in which the scrotal and abdominal integument is used to replace the deficient anterior vesical wall, has been so far perfected as to furnish a means of providing a receptacle for the urine, but at present no means exist for retaining the urine within the newly-formed cavity except of a mechanical kind.

With the object of diverting the flow of urine from the anterior surface of the abdomen and leading it into the rectum, various operations have been undertaken.

Mr. Lloyd and Mr. Athol Johnstone attempted unsuccessfully to establish a direct communication between the posterior wall of the bladder and the cavity of the rectum by means of a seton, but in both cases the patients died from injury to the recto-vesical pouch of the peritonæum.

Mr. Holmes succeeded in establishing the desired passage between the bladder and rectum without injury to the peri-

Fig. 1.—First published report of attempt to implant ureters into colon. (St. Barth. Hosp. Rep. 15: 29-35, 1879.)

to freed anal mucosa within the anal sphincter. By this method it was hoped to secure continence through the action of the anal sphincter. At a second stage the ureters were implanted into the upper end of the ileal pouch. Three such operations were described for extrophy with one death and the 2 survivors had urinary fistulas.

The method of Seiffert[19] was described in 1937 but may have been published earlier. This author isolated a jejunal segment, brought the lower end through the abdominal wall in the right lower quadrant, and implanted both ureters into the upper end of the segment.

In recent years Bricker has used a segment of lower ileum in a similar manner. He has implanted the ureters into the pouch by mucosa-to-mucosa anastomosis end-to-side after closure of the upper end of the isolated segment of bowel (Fig. 3). A suitable bag sealed to the skin about the stoma is worn by the patient. Between 1950 and 1954 Bricker[3] employed this type of urinary diversion in 106 cases and reported considerable satisfaction with it. Cordonnier,[10] Annis, Hunter, and Wells,[1] among a number of others, confirmed Bricker's observations and found the method highly satisfactory. However, Cordonnier stated that following removal of the bladder he implants the ureters into the remaining intact colon.

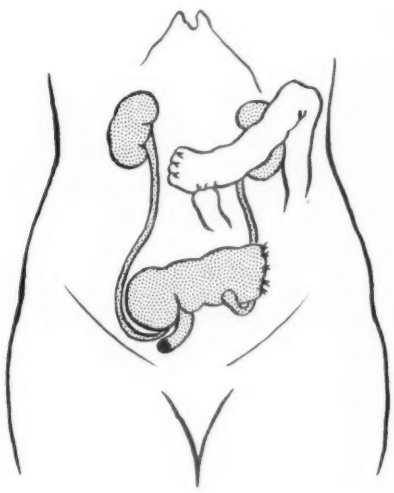

Fig. 2.

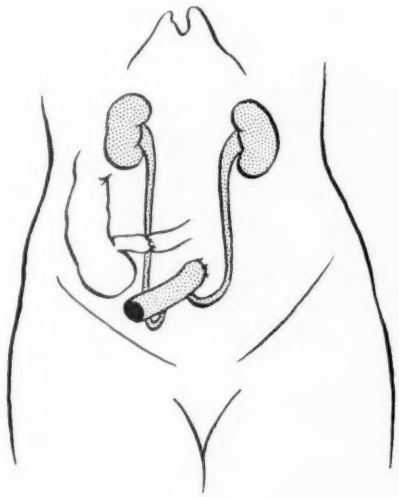

Fig. 3.

Fig. 2.—Bladder substituted by cecum and ascending colon. Lowest segment of ileum serves as external conduit.

Fig. 3.—Bladder substituted by isolated lower segment of ileum. Ureters implanted end-to-side.

One of us (A. B.) has utilized isolated segments of ileum in the aforedescribed manner with certain modifications. Frequently the lowest segment of ileum is isolated and the stump of ileum on the cecum is invaginated by purse-string sutures in a manner similar to the invagination of an appendix stump. Continuity is re-established by ileocolostomy employing the ascending colon. The ureters are implanted into the upper end of the ileal segment by the technique illustrated in Fig. 4. By this method the isolated ileal segment assumes a vertical position and the stoma is brought out through the abdominal wall in the midline when the colon remains intact. Following total pelvic exenteration, an end colostomy is made in the left lower quadrant, and the ileal stoma is placed in the right lower quadrant.

Other members of the senior author's service are utilizing a segment of ileum as described by Bricker and note satisfaction with the procedure.

In the older literature are records where a segment of ileum was isolated, ureters were implanted into it, and the lower end of the segment was anastomosed with some portion of the colon, thus interposing a segment of small bowel between ends of ureter and colon. In Blair's case (1916) the ileal segment was anastomosed to the ascending colon. Moskowitz in 1909 implanted the segment into the transverse colon as did Spannaus in 1911. In 1907 Berg anastomosed such segments into the upper pelvic colon. It is of interest that the latter principle is now revived by Hudson and Fox[12] who reported 3 instances and by Turnbull and Higgins[20] who have used it in 8 cases. The latter authors emphasize the implantation of the lower end of the ileum into the sigmoid in such a manner that it protrudes (intussuscepts) into the colon, thus affording a valve-like structure that tends to obviate reflux into the segment of ileum.

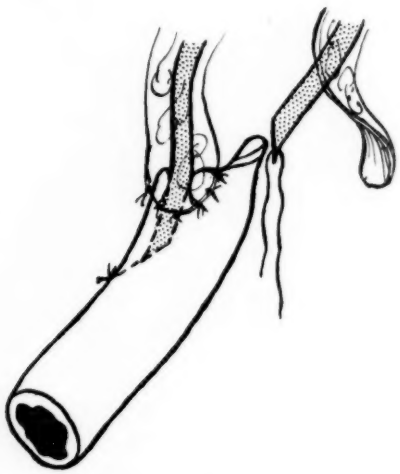

Fig. 4.

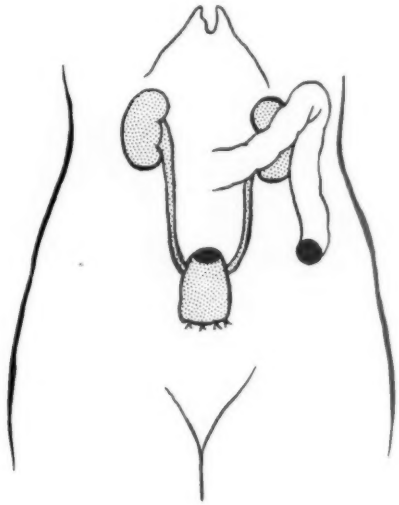

Fig. 5.

Fig. 4.—Isolated lower segment of ileum for bladder substitution. Ureters have been spatulated and are drawn into upper open end by retaining suture. Drawing ureter into open end of bowel invaginates bowel mucosa about it. Peritoneal strip retained on ureter to use as patch over implantation site. Lower open end of bowel brought through abdominal wall.

Fig. 5.—Bladder substituted by isolated pouch of sigmoid colon.

BLADDER SUBSTITUTION BY USING ISOLATED SEGMENT OF DESCENDING COLON OR SIGMOID

Following pelvic exenteration a reservoir for urine may be readily fashioned by transection of transverse or descending colon in its mid or lower portions with closure of the distal end of the lower segment, thus forming an isolated colon pouch. The distal end of the upper segment is brought out as an end colostomy, the upper end of the isolated segment is brought out either adjacent to the end colostomy (double barrel) or with the end colostomy in the left lower quadrant, and the upper end of the isolated lower segment is brought out in the midline (Fig. 5). The ureters are implanted into the isolated colon pouch. Another method is to close the upper end of the isolated sigmoid pouch, implant the ureters into the pouch end-to-side, and bring the lower end of the pouch out as the urinary fistula (in the midline).

This particular principle, that is, utilization of a distal isolated colonic segment for urinary reservoir with its own separate opening, is one that does not seem to have been suggested and actually essayed by the older authors since it is not discussed in the exhaustive review by Hinman and Weyrauch.[11]

In recent years this principle apparently has been utilized successfully by some surgeons (Parsons[17] and Cade[9]). The advantages would seem to be ease of executive and separation of fecal and urinary streams.

BLADDER SUBSTITUTION BY USING RECTAL COLON AND INTACT SPHINCTER WITH END COLOSTOMY ABOVE

The first clinical application of this principle was made by Remedi in 1905, again by Kroenig in 1907, and by Rovsing in 1915. In all, 8 patients were operated upon in this manner.

Fig. 6.—Bladder substituted by isolated intact rectal colon with diversion of fecal stream by end colostomy—"rectal bladder." Ureters implanted into rectal colon.

Beginning in 1953 on the senior author's service, 11 patients who received anterior pelvic exenteration also had urinary diversion by means of a "rectal bladder"[6] and conventional end colostomy above this (Fig. 6). The ureters were implanted into the closed rectal pouch in an end-to-side manner or directly into the upper end. The advantages of the method are that the wearing of a bag on the anterior abdominal wall is obviated while the management of an end colostomy is relatively simple and that urinary excretion is under control (by the intact anal sphincter). The disadvantage is that the patient may have frequent desire to empty the lower colon (urinate) unless the lower segment is left relatively long. Another disadvantage is that in the event of recurrences of cancer in the pelvis, the rectal bladder may be involved and thus urinary excretion compromised. Furthermore such recurrences may lead to fistulization of the rectal bladder with obvious distressing complications due to uncontrolled leakage from below. Recently instances of this procedure following total cystectomy also have been reported by Kinman and associates[15] and Paull and Hodges[18] with satisfactory immediate results in a total of 13 patients.

BLADDER SUBSTITUTION BY USING ISOLATED TERMINAL RECTAL COLON IN COMBINATION WITH PULL-DOWN OF SIGMOID THROUGH ANAL SPHINCTER

In 1898 Gersuny isolated the lower rectum, implanted ureters in the pouch, and then drew the lower sigmoid downward through the anal sphincter anterior to the anus. In 1910 Heitz-Boyer and Hovelacque carried out the same procedure in principle but excised the coccyx and drew down the sigmoid posterior to the anus. Similar operations were performed by Lastaire in 1913, Melnikoff in 1924, and Mikuli in 1930.

Recently, in 1956, Johnson[13] reported a personal series of 17 cases in which the isolated terminal rectal colon with intact anus was used for the urinary reservoir by implantation of the ureters. The lower end of the transected sigmoid was drawn downward anterior to the anus through the anal sphincter and sutured to the perineal skin (Fig. 7). Urinary and fecal continence are said to have been achieved and this author reports satisfaction with the method. A similar procedure was reported successful in 4 young children by Kiefer and Linke[14] (extrophy of the bladder). In none of them was electrolyte imbalance noted during a 6 to 9 months' postoperative follow-up.

Fig. 7.

Fig. 8.

Fig. 7.—Bladder substituted by isolated rectal colon with implantation of ureters. Sigmoid drawn into perineum as colostomy, within anal sphincter to afford fecal continence.

Fig. 8.—After total pelvic exenteration ureters are implanted above end colostomy—"wet colostomy."

THE WET COLOSTOMY

When all pelvic viscera have been excised, urinary diversion may be carried out by implantation of the ureters into the colon at varying levels proximal to the end colostomy. This situation was described by Brunschwig[5] in 1948 and the term "wet colostomy" was applied to it because in contrast to the usual colostomy which can be "educated" to function at intervals depending upon a set plan of irrigation, the wet colostomy discharges urine more or less constantly and fecal material intermittently. It is necessary to wear a bag sealed to the skin about the stoma. In 1950 Appleby[2] reported excision of rectal colon, bladder, and prostate with implantation of one ureter into the cecum and one into the sigmoid above an end colostomy.

Under these conditions the colon while functioning for the excretion of bowel contents also functions as a reservoir for urine. The latter may pool up to varying levels of the colon, even to the cecum. Voluntary control of excreta is not possible.

The advantages of the wet colostomy are ease and simplicity of performance and the fact that the patient has only one ostomy to care for. Disadvantages include odor and at times "messiness" when bags are changed. With time the problem of odor has been surmounted by suitable bag material and deodorants.

The senior author and collaborators[7] on his service have performed 240 wet colostomies and experience has shown that adjustment by the patient to it is usually possible. The likelihood of hyperchloremic acidosis producing symptoms is minimal.

With this form of urinary diversion patients have been returned to full physical activities. In some instances even under the most adverse living conditions patients have devised for themselves "wet colostomy bags" that have functioned satisfactorily and worn while they were gainfully employed outside the home.

URETEROINTESTINAL ANASTOMOSIS

It is beyond the scope of this article to discuss the techniques of ureterointestinal anastomosis. It would appear, however, that in modern practice those methods which entail some form of long tunnelling in the bowel wall preliminary to entrance of the ureter into the bowel seem to be employed less frequently. Stricture at the site of implantation is a major hazard. Likewise fear of leakage often leads to excessive suturing at the implantation site. More and more, surgeons seem to be performing some type of mucosa-to-mucosa anastomosis with minimal banking up of tissue at the site, first described as mentioned by Smith in 1879.

The senior author[8] has persisted in a simple method previously described, the principle of which is to cut a small circular opening in the bowel wall, threading the spatulized ureter into the bowel by means of a silk retaining suture, both ends of which are brought through the bowel wall and tied (Fig. 9). Three or four interrupted catgut sutures are taken between periureteral tissue and bowel mucosa. A strip of peritoneum 2 or 3 cm. in diameter is retained along the ureter (but not carried into the bowel) and after ureteral implantation is sutured over the implantation site as a "sealing patch." Another principle is to see to it that, once the ureter has been threaded into the bowel, the end of a small hemostat can be slipped easily into the lumen of the bowel between ureteral wall and edge of the opening into the bowel. It is to be remembered that shortly after mobilization the transected end of the ureter becomes edematous and this serves to plug off the opening and prevent leakage. Still another principle is to avoid traction on the ureters no matter how satisfactory the implantation appears to be. This is possible by appropriate suturing of the bowel to peritoneum, mesenteric stumps, and so forth in the operative field to relieve stress at the implantation sites.

DISCUSSION

Which is the most satisfactory method for urinary diversion with creation of a urinary reservoir (or "artificial" bladder)?

No hard and fast recommendations can be made at this time. In the foregoing discussion only those methods are described that have been discussed in recent years and reported by various authors as affording some measure of satisfaction in their hands. The choice of which method to employ is governed by a variety of factors. First, it depends upon the individual operator as to his personal preference, the one which in his hands proves satisfactory and has proved satisfactory to his patients. As his experience increases his conceptions will change and his methods may alter. At present no one surgeon has a very large experience with each of these varied methods. *No method is free from complications.* As experience of any one surgeon increases his personal incidence of complications will increase and as a result his methods may be changed. In Table I, the various types of urinary diversion carried out to date on the senior author's service are summarized.

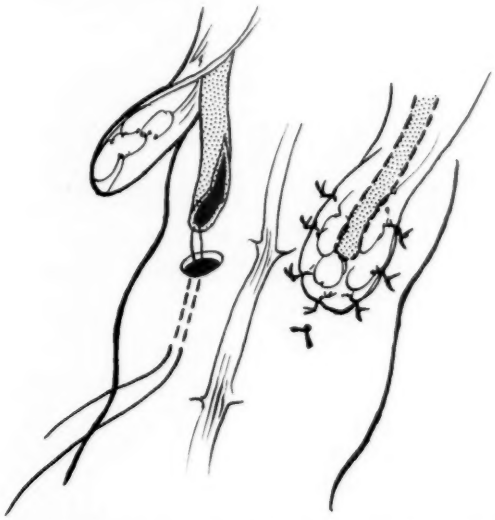

Fig. 9.—Diagram of method of ureterocolic anastomosis. Circular opening made in bowel wall. Ureters isolated with adherent strip of peritoneum. Spatulized ureter drawn into bowel and implantation site sealed by patch of peritoneum. Silk technique except for catgut sutures between bowel wall and periureteral tissues.

TABLE I. TYPES OF URINARY DIVERSION EMPLOYED IN 549 CASES OF PELVIC EXENTERATION (September, 1947 to January, 1958)

OPERATION	TOTAL EXENTERATION	ANTERIOR EXENTERATION	TOTALS
Ureterocolic anastomoses	240	142	382
Cutaneous ureterostomies	55	15	70
Ileal conduits ("Ileal bladder")	25	28	53
"Rectal bladder" (with end colostomy)	0	11	11
Miscellaneous (one ureter in colon and one cutaneous ureterostomy, etc.)	14	5	19
Brief survivors (various types)	12	2	14
	346	203	549

Another factor in choice of methods is the patient him- or herself, the social status, the attitude of the family, the problems to be faced after hospital

discharge and so forth. An important factor is the availability of medical supervision. None of these patients should be discharged and not carefully followed. The situation of a closed clean operative wound, on the one hand, and the consequence of urinary diversion with creation of some type of urinary reservoir, on the other hand, cannot be compared. Where patients must travel a distance from the one who operated upon them, sympathetic and careful medical supervision near home must be planned for and secured if possible. It is not always easy to secure interested supervision for patients operated upon in this fashion from physicians at a distance who may be seeing the patient for the first time and may not be familiar with the procedures carried out and their possible complications.

In the older records concerning ureterointestinal anastomosis the problem of electrolyte imbalance was not touched upon. This is understandable because of the lack of clinical laboratories in the past not to mention the nonexistence of methods for blood chemical analyses and so forth. The modern appreciation of hyperchloremic acidosis and so on in connection with the afore-mentioned operations has greatly enhanced the over-all conception of the physiologic disturbances incident to them. The exact mechanisms for the production of this situation (elevated blood urea and plasma chlorides and lowered CO_2 combining power) are not yet fully understood, although its development in each patient is sought for and measures are instituted to rectify it. It would appear that after all such operations there is some likelihood that it will occur. It appears that hyperchloremic acidosis may be present but not manifested as a clinical disturbance whereas in other instances symptoms which may be severe are encountered. It would appear that the likelihood of hyperchloremic acidosis is enhanced if there is some degree of obstruction or sphincter control to the excretion of the diverted urinary stream, or if the kidneys in some way are damaged (secondary to infection or ureteral obstruction).

With increasing experience and constant discussions, more and more will be learned by each surgeon for the benefit of all.

The feasibility of the procedures is being constantly demonstrated by the increasing numbers of 5-year survivors and by those who are approaching the tenth postoperative year, living comfortable, active, and useful lives. Furthermore, new problems are being created by these patients, such as continued clinical well-being with progressive elevation of blood urea nitrogen, continued clinical well-being with blood chemical evidence of hyperchloremic acidosis, and progressive hydronephrosis (up to a point), and so forth. The evaluation of these patients for continued observations or for reoperation to redivert the urinary tract constitutes a complex situation which only continued experience and study will help to elucidate.

The principal objective of radical multivisceral excisions in the pelvis is to eradicate advanced cancer. Often these become long and tedious procedures and often the patient's condition during the operations may become precarious and necessitate as rapid a termination of the procedure as possible. In the latter event the creation of bladder substitutes by isolated segments of small bowel

prolong the operations. Rapid termination of the procedure is possible by cutaneous ureterostomies or by formation of a wet colostomy in the event of total pelvic exenteration.

It is generally inferred that present-day surgery for diversion of the urinary tract is greatly facilitated by the advent of chemo- and antibiotic therapy. These agents have proved especially effective in urinary tract infections. However, it must be recalled that ureterosigmoidostomy was carried out successfully in a series of patients with extrophy and severe hypospadias by Grey Turner[21] with survivals from 8 to 19½ years and by others before the advent of modern antimicrobial therapy. It goes without saying, however, that chemotherapy and antibiotic therapy now are indispensable with operations for urinary diversion.

Once the cancer has been controlled the principal problem becomes one of urinary tract maintenance. The problems of renal physiology and pathology under such altered conditions assume a role of paramount importance for the long survival of these patients.

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APPLICATION OF AUTOGENOUS SKIN GRAFTS TO THE GASTRIC WALL

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REPLACEMENT of the gastric mucosa by nonacid-bearing epithelium has been proposed as an experimental surgical approach to the peptic ulcer problem.[1, 2] It has been considered that ablation of the gastric mucosa might effectively obliterate the production of acid-peptic secretion and at the same time retain reservoir function without disturbance of motility. Stripping of the gastric mucosa from the gastric wall may be accomplished without damage to the muscular wall.[4] When dogs were used, it was found that the gastric mucosa regenerated in 3 to 6 weeks so that the defect, created by stripping, was covered even though large areas of the gastric wall were denuded.[4] Return of secretory function was diminished initially but gradually returned after several months.[3] The regeneration of mucosa was found to occur from islands of mucosa which were left adherent to the submucosa. A species difference was noted when cats were subjected to similar experiments. In these the level of stripping was accomplished most readily at the muscularis mucosa and residual mucosa was not left behind. Consequent contraction and stenosis of the stomach occurred.[4] Histologic studies of the human stomach, when stripped distal to the line of resection at the time of partial gastrectomy, indicated that the level of stripping in the human stomach is similar to that of the cat.

It would appear that stripping of the mucosa from the gastric wall should be accompanied by the application of some other mucosal or epithelial surface to the denuded area of the stomach. For this purpose, free mucosal-submucosal autografts of jejunal mucosa[2] and split-thickness skin grafts[1] have been placed in the operative defect after stripping. The survival of such grafts has been reported although the amount of skin that has persisted varied greatly.

The present report is a description of the experience which has been obtained with the grafting of skin in the stomach after mucosal stripping. Because the survival of skin was discouraging in the experiments in which dogs were used, pigs were employed in similar studies.

METHODS

The technique of gastric mucosal stripping has been described in detail previously.[1, 4] The essential aspects are included for orientation. In dogs,

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intravenous Nembutal anesthesia has been employed. Anesthetic problems are greater in pigs and a different technique was developed. Obstruction to the airway occurred easily and these animals appear to be quite sensitive to Nembutal. The pigs were 6 to 8 weeks of age and weighed from 20 to 25 pounds. Anesthesia was induced with 3 to 6 c.c. of sodium pentobarbital by intraperitoneal injection. A No. 20 endotracheal tube was passed and anesthesia was maintained with ether and oxygen. Intravenous fluids, usually 500 c.c. of 5 per cent dextrose in distilled water, were administered through an ear vein during the operative procedure. Whole blood transfusions are not feasible in pigs because there are a large number of blood groups.

Autogenous skin grafts were taken from the anterior abdominal wall, both in dogs and pigs, by means of a Reese dermatome. The split-thickness grafts varied from 0.008 to 0.012 inch in thickness and were applied to the denuded gastric wall with interrupted and continuous sutures of fine silk.

After operation, oral feedings were begun on the third day after operation. Penicillin and dihydrostreptomycin were given intramuscularly daily for 5 days following operation.

Operation was performed again in the dogs at intervals from 4 to 12 weeks after application of the skin grafts. Biopsy of the gastric wall was performed or the animals were sacrificed. Estimates were made of the percentage of the amount of survival of skin graft. In an attempt to test the functional activity of the grafted stomach, 20 dogs were subjected to the Mann-Williamson operation. Estimates of the extent of survival of skin in the stomach were made at the time of the performance of the Mann-Williamson procedure and at the time of death or sacrifice. The pigs were maintained on an unrestricted diet after one week and were sent to a farm. The rapid growth of these animals makes prolonged management difficult. The pigs were allowed to survive from 5 to 16 weeks (average 9.5 weeks) and were then subjected to autopsy study.

RESULTS

Gastric mucosal stripping and application of split-thickness autogenous skin grafts were performed in 31 dogs and 22 survived the operative procedure. The longest period of observation was 7 months and the average duration of survival between operation and autopsy was 6.3 weeks. The amount of skin that survived ranged from an absence of skin to 80 per cent and averaged 15 per cent. Gross and microscopic study of the area that had been stripped of mucosa including the grafted site demonstrated regeneration of the gastric mucosa (Fig. 1). In 7 of these animals that were allowed to survive for more than 11 weeks after gastric skin grafting, only two were found to have persistent epidermal elements and in these only small fragments of skin remained.

Vagotomy and pyloroplasty accompanied application of skin grafts to the denuded gastric wall in 11 dogs. This procedure was employed in an attempt to obtain improved survival of skin by decreased activity of the gastric

wall. However, an improvement in "take" of the skin grafts was not obtained. The average survival was estimated as 13 per cent in this group which was studied for an average period of 8.2 weeks.

Of the 20 dogs in which the Mann-Williamson procedure followed gastric stripping and skin grafting, 8 survived sufficiently long to be evaluated. In these 8 dogs, the Mann-Williamson procedure was undertaken 6 to 43 weeks after the skin grafts had been applied to the stomach and were then observed for periods which ranged from 8 to 12 weeks. Peptic ulceration appeared in 4 animals, one of which died of perforated jejunal ulceration. Evidence of ulceration was absent in the other four. The amount of surviving skin was diminished in all at the time of autopsy examination and averaged less than 5 per cent.

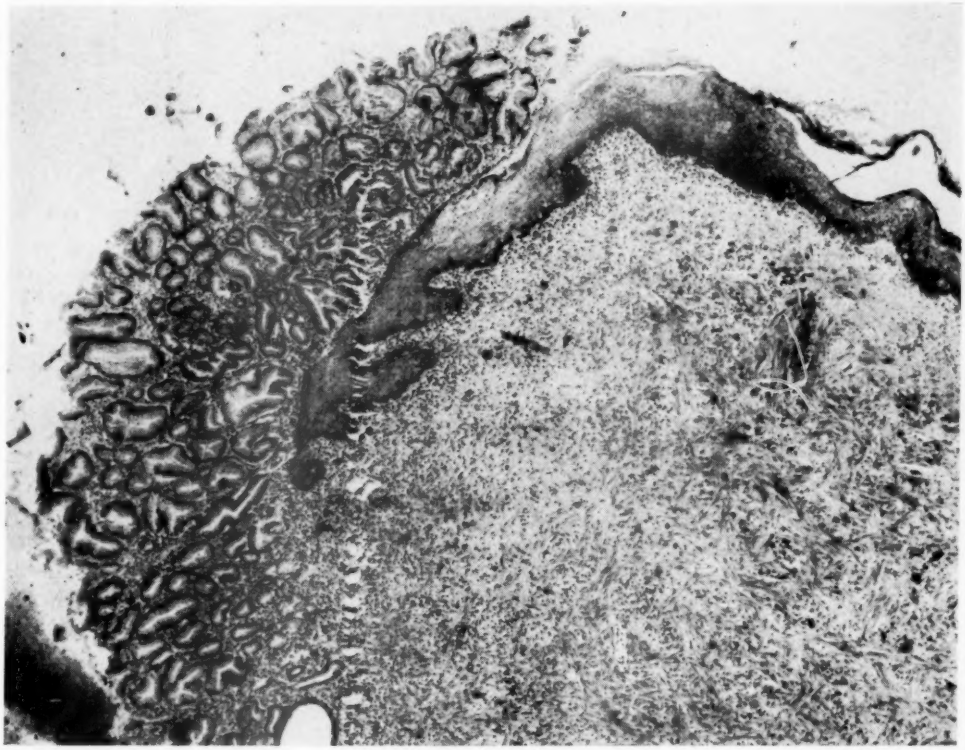
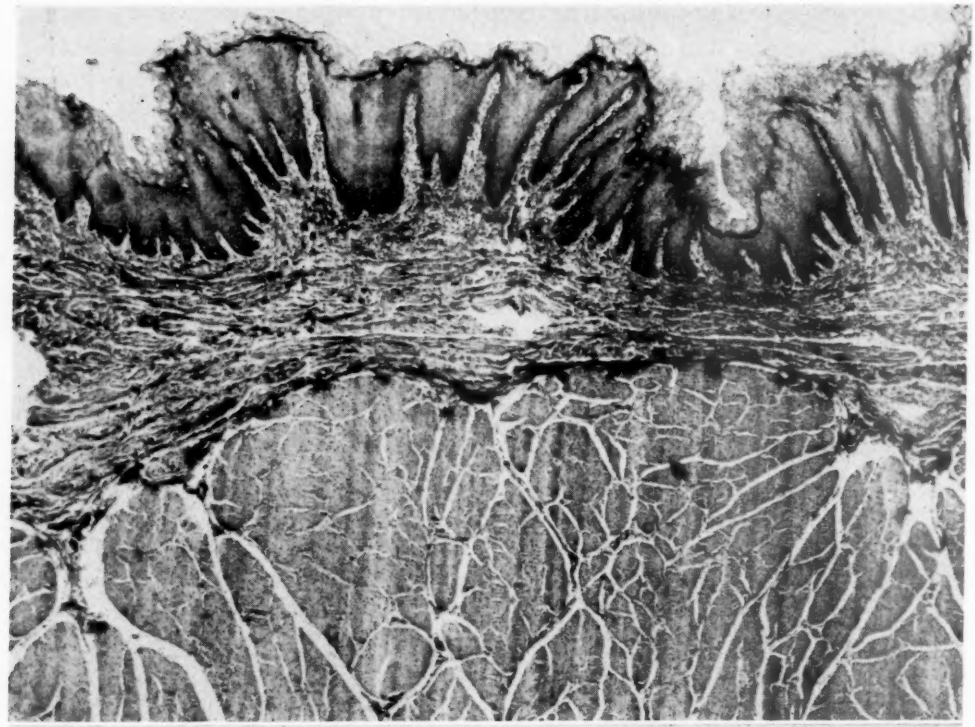


Fig. 1.—In this photomicrograph the junction of the skin graft and the regenerating gastric mucosa may be seen. In this section from a dog, the gastric mucosa appears to be proliferating and growing over the grafted skin.

Twenty-one pigs were subjected to the procedure of gastric mucosal stripping and skin grafting. In the early phases, the mortality rate was high due to anesthetic difficulties so that only 9 of the 21 pigs survived. The nutritional state of the pigs remained good and growth was satisfactory. Gross and microscopic examination of the stomach at the time of autopsy demonstrated survival of skin at the recipient site in 8 of the 9 pigs (Fig. 2). In one animal a hematoma under the graft had apparently caused a failure. The average survival of the skin grafts was 45 per cent and in 2 animals that had been followed for 12 and 16 weeks after application of the gastric skin grafts, the

entire skin grafts had appeared to survive. One pig died 5 weeks after operation from pyloric obstruction. Fifty per cent of the graft had survived but inadvertently the skin graft had been placed in the pyloric canal and caused pyloric obstruction.

Fig. 2.



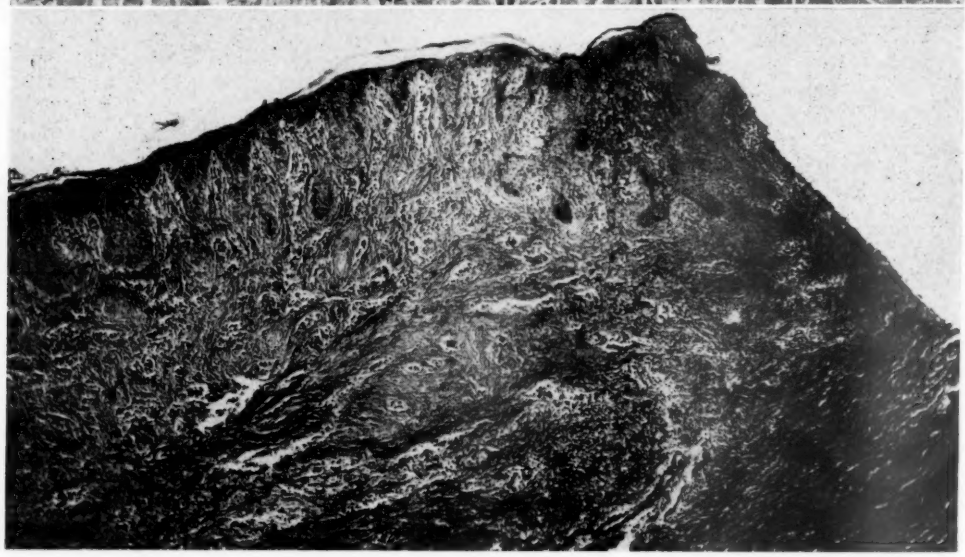
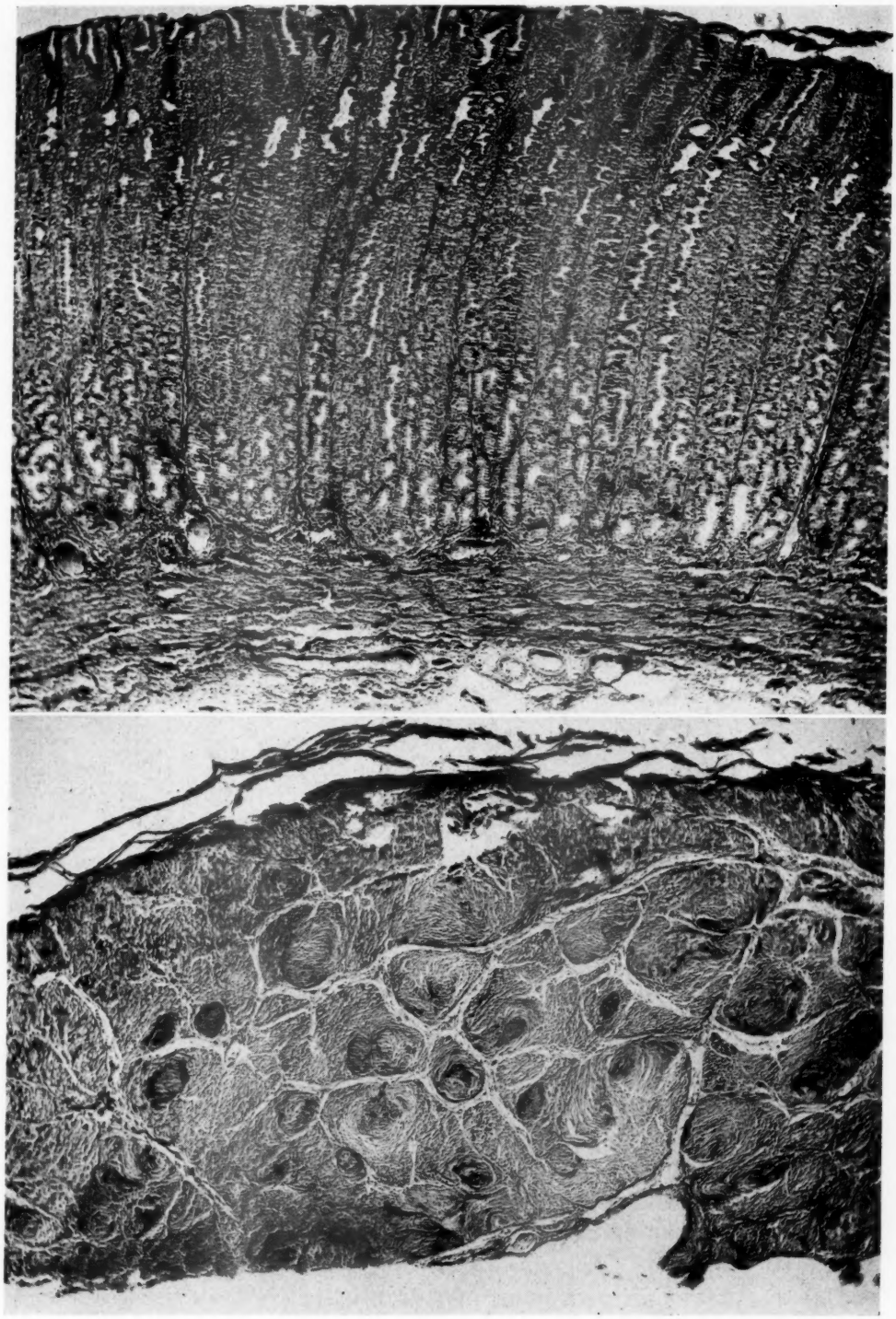


Fig. 3.

Fig. 2.—Microscopic section from the gastric wall of a pig which was obtained 10 weeks after skin grafting. The autogenous skin graft appears healthy and without evidence of erosion.

Fig. 3.—This low-power view demonstrates the junction of the skin graft with the denuded gastric wall of the pig 8 weeks after the application of the graft. Evidence of regeneration of gastric mucosa is absent.

A.



B.

Fig. 4.—*A*, Microscopic examination of the mucosa which has been stripped from the gastric wall of the pig demonstrates that the muscularis mucosae is removed with the mucosa. *B*, Microscopic study of the denuded gastric wall of the pig fails to demonstrate evidence of residual islands of gastric mucosa attached to the muscular wall.

Gross examination of the stomach in the pig gave evidence of some contraction of the stomach about the denuded portion but gastric capacity was well preserved. Microscopic study did not demonstrate regeneration of gastric mucosa across the portion of the stomach from which the mucosa had been removed. Where the skin graft did not cover the stripped gastric wall, the serosal and muscular elements were covered by fibrous tissue and inflammatory cells. There was a sharp line of demarcation between the edges of the grafted skin and the bare gastric wall and between the bare areas and the margin of the gastric mucosa. The skin grafts did not demonstrate evidence of digestion or ulceration and appeared to be adherent to the underlying submucosa without inflammatory reaction (Fig. 3).

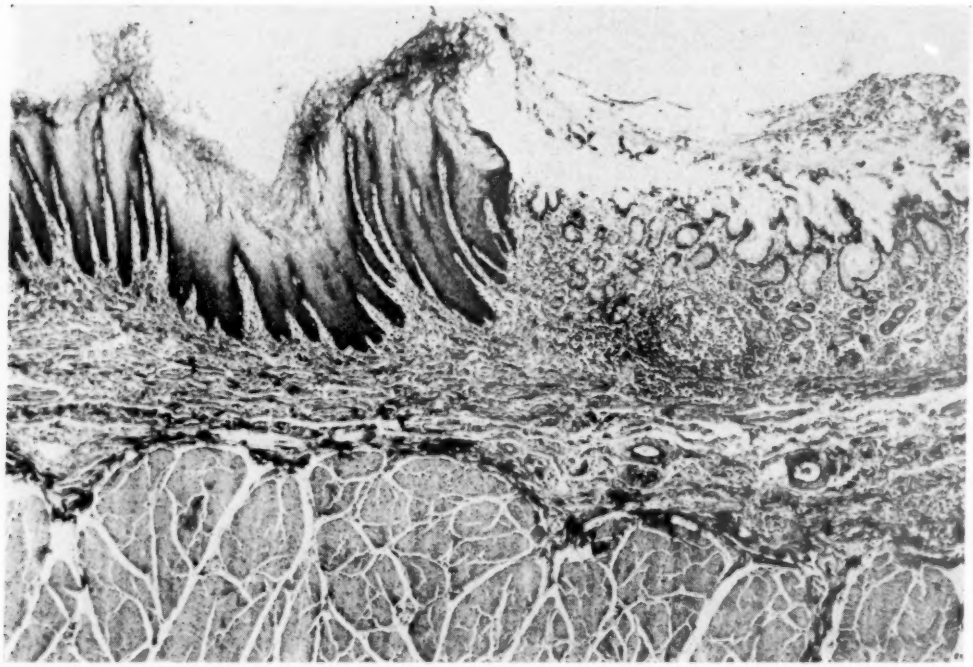


Fig. 5.—The junction between the autogenous skin graft and the gastric mucosa in a pig is demonstrated 10 weeks after grafting. The skin appears viable and healthy and there does not seem to be undermining of the skin graft by the gastric mucosa.

DISCUSSION

In the previous report,[1] certain problems were noted which are inherent to application of split-thickness skin grafts to the denuded gastric wall. These include immobilization of the graft site in a muscular organ, hematoma formation beneath the graft, displacement of the graft by regeneration of adjacent mucosa, and accumulation of gastric secretion from remnants of gastric mucosa beneath the graft. Immobilization has been attempted by inflated balloons, by the placement of a bolus of cotton or gauze over the graft, and by vagotomy, but the survival of the grafts did not seem to be influenced by these measures. Although bleeding occurred at the time of gastric stripping, hematoma formation has been encountered infrequently. The most important factor in the failure to obtain consistent survival of the skin grafts on the

gastric wall of the dog has been related to failure to ablate the gastric mucosa when stripping is undertaken. Islands of mucosa remained and seemed to be responsible for loss of the skin grafts. These persistent glands appear to cause failure of the graft by the secretion of gastric juices beneath the graft and by the outgrowth and coalescence of the glandular elements in regeneration of the mucosa.

The utilization of the pig would appear to overcome these obstacles (Figs. 4, *A* and *B*, and 5). A difference among species had been noted in an earlier report when removal of the gastric mucosa in the cat was not followed by mucosal regeneration; in dogs, regeneration was present within 3 to 6 weeks after stripping. The stomach of the pig resembles that of the cat in this regard. The importance of this difference is seemingly reflected in the higher incidence of survival of skin after application of skin grafts to the wall of the stomach of the pig. The graft appeared to have a salutary effect in the prevention of cicatricial narrowing of the stomach and consequent loss of capacity, which had occurred in the cat.

These experiments suggest that the application of autogenous skin grafts to the gastric wall after ablation of the mucosa by stripping may be expected to be followed by a higher incidence of survival of skin in the pig than in the dog. These experiments, however, do not yield any information on the effect of this procedure upon the secretory capacity of the stomach. Further studies are needed to clarify this aspect of the problem.

SUMMARY

Experiments have been described in dogs and pigs in which the gastric wall has been denuded by stripping the mucosa from the underlying submucosa and muscularis. The defects have been covered by autogenous split-thickness skin grafts.

In 22 dogs, the amount of skin that survived averaged 15 per cent of the original graft that had been applied. There was evidence that regeneration of the gastric mucosa contributed to loss of the grafted skin.

Nine pigs were subjected to a similar experiment. Loss of the grafted skin occurred in one of these as a result of hematoma formation beneath the graft. The average survival of skin in the stomach was 45 per cent in the remaining 8 pigs, and in 2 the entire skin graft was found viable 12 and 16 weeks, respectively, after application.

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CUL-DE-SAC SMEARS FOR CANCER CELLS

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INTRODUCTION

RECENT studies appearing in the medical literature have revived interest in and focused attention on the problem of cancer-cell spillage and implantation of tumor cells during surgery for carcinoma. Cancer cells have been recovered from wound washings,[6-8] margins of resected colons,[1, 5] and mesenteric venous blood during colon resections,[3] and therefore it might be assumed that these areas are a dangerous source of cancer-cell seeding during operation. Credible as this fact may be, it is only fair to point out, on the other hand, the conclusions of another investigator,[2] who found that there is "no significant difference between the number of cells (in the mesenteric venous blood) before and after manipulation of the rectal or colon cancer," and that "no prognostic data can be derived from the finding of cancer cells in the venous blood from the tumor area." Others have progressed to the extent of attempting to destroy by chemical means tumor cells which may have been exfoliated during operative maneuvers at the time of surgery for intra-abdominal carcinoma.[4]

With these thoughts in mind, the present study is undertaken in an attempt to detect the presence or absence of tumor cells in the peritoneal cavity of patients with cancer of the colon and rectum, prior to operative manipulation. If such cells exist, what is their significance, if any?

METHODS AND MATERIALS

A simple procedure was devised in which some of the intraperitoneal fluid collected in the cul-de-sac is smeared on microslides. This is done as soon as the abdominal cavity is entered. With the small intestines packed into the upper abdomen, the pelvic floor is exposed and a sterile, finely meshed, cotton "stick-sponge" is used to swab the cul-de-sac. After the glass slide is smeared with the sponge, it is immediately immersed in a solution containing equal parts of 95 per cent alcohol and ether. The slide is then stained in the usual Papanicolaou fashion, screened by a cytotechnician, and verified by a cytologist.

Over the past 1½ years, the surgical staff of the Rectum and Colon Service at the Memorial Center has collected a consecutive series of 180 such smears. Except for the occasional case, all these patients had carcinoma of the colon and rectum.

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RESULTS

Crude as this simple method in the collection of cul-de-sac smears may seem, the over-all results in 180 cases are summarized in Table I.

TABLE I. RESULTS

	CASES	PER CENT
Inadequate technologically	47	26
Benign cells only (negative)	60	33
Suspicious	40*	22
Malignant cells (positive)	33**	19
Total	180	100

*One case each of carcinoma of breast and pancreas.
**One case each of carcinoma of breast, corpus uteri, pancreas and unknown primary.

Forty-seven (26 per cent) microscopic smears were considered technologically too poor for cytologic evaluation. Sixty (33 per cent) revealed benign cells only. Forty (22 per cent) demonstrated cells suspicious for carcinoma. Thirty-three (19 per cent) were interpreted as showing malignant cells.

CYTOLOGIC DISCUSSION

Swabs of the cul-de-sac in cases free of cancer usually yield rather scanty smears containing blood, leukocytes, macrophages, and mesothelial cells from the peritoneum. It is these last-named that chiefly concern the cytologist, since they appear to be the easiest to confuse with cancer cells, particularly in poorly preserved specimens. These cells are usually of moderate size, with oval nuclei having fairly bland and uniform structure; they are seen in large sheets of an epithelial appearance and also in small clumps and singly (Figs. 1 and 2). Degenerative changes, particularly those following drying, may cause enlargement, distortion, and obliteration of pattern of the nuclei and thus lead to confusion with cancer cells (Fig. 3).

In cases where cancer cells are demonstrated (Figs. 4-6), they appear as single cells or clusters of cells having the classical changes associated with malignant nuclei present in varying degree: irregularity in shape, variation in size within the same cluster, prominent nucleoli, coarseness and irregularity of chromatin pattern, and hyperchromasia. Like adenocarcinoma elsewhere, cancers of the large bowel may show these changes only relatively subtly, and in poorly preserved cells they may be very difficult to detect. The characteristic smearing-out of carcinoma, with its lack of cohesiveness among cells, is sometimes helpful.

In the present series, where serious doubt remained as to a smear's being negative or positive, the usual reason was poor preservation of the specimen, and therefore the need for careful smearing and immediate fixation is urgent, if evaluations of such material are to be reliable.

COMMENTS

Discarding the 47 technologically bad smears, there remain 133 for analysis and clinicopathologic correlation.

Fig. 1.

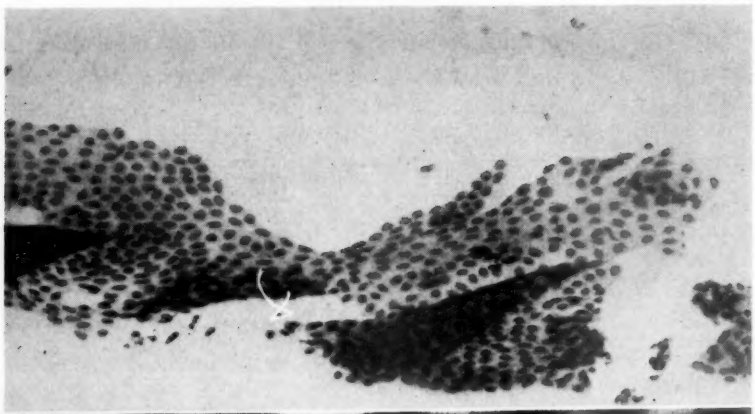

Fig. 2.

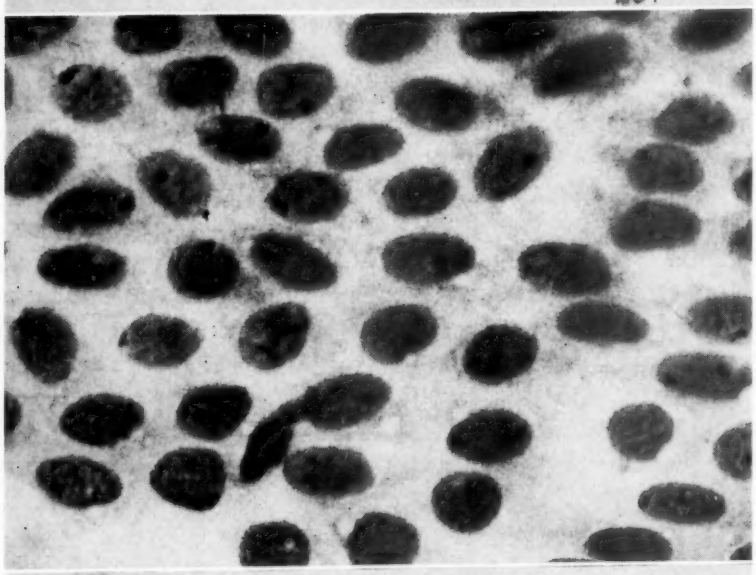

Fig. 3.

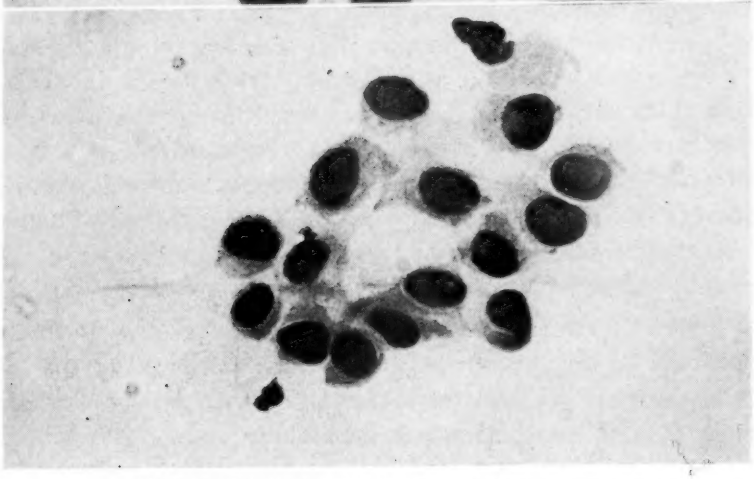

Fig. 1.—Benign cells (low power).
Fig. 2.—Benign cells (high power).
Fig. 3.—Poorly fixed probably benign cells.

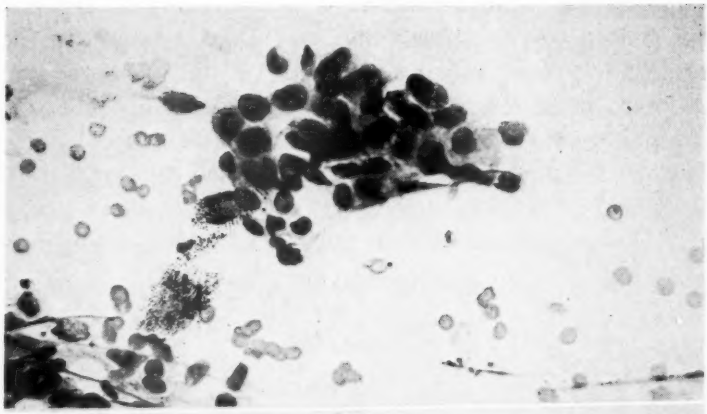

Fig. 4.

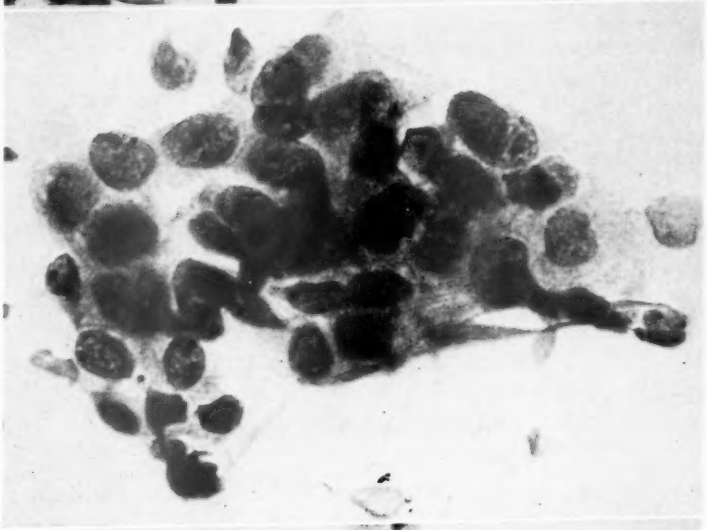

Fig. 5.

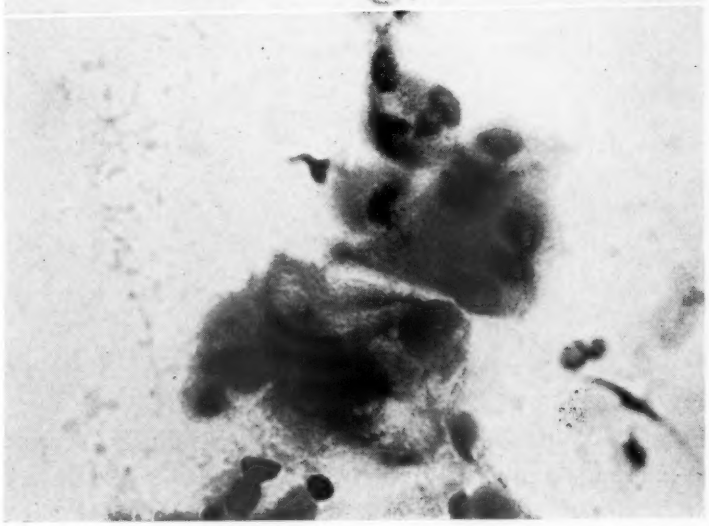

Fig. 6.

Fig. 4.—Cancer cells (low power).
Fig. 5.—Cancer cells (high power).
Fig. 6.—Cancer cells.

As is to be expected, the recovery of positive smears was more likely in the presence of gross liver metastasis and/or tumor implants in the peritoneum or on the serosa of the intestinal tract. Conversely, absence of disease in these areas yielded many more negative smears. Interestingly enough, however, 8 patients with no obvious gross evidence of metastatic cancer in the abdominal cavity revealed cul-de-sac smears positive for tumor cells and 27 such patients yielded suspicious smears. There were only 2 false-positive and 4 false-suspicious smears. Fifteen patients who had visible intraperitoneal metastasis failed to yield positive or even suspicious smears (Table II).

TABLE II

	POSITIVE (33)	SUSPICIOUS (40)	NEGATIVE (60)
Gross liver metastasis and/or serosal and peritoneal implantation	23	9	15
Liver, serosa, and peritoneum free of gross disease	8	27	36
No primary cancer at all (diverticulosis, polyps, fibroid uterus)	2	4	9

Individual characteristics of the carcinoma, such as anatomic location, mesenteric lymph-node metastasis, and histologic grade, did not seem to have any bearing on the smear result. These data are recorded in Table III.

TABLE III. OTHER CORRELATION

	POSITIVE (33)	SUSPICIOUS (40)	NEGATIVE (60)
Anatomic location			
Rectum (below 10 cm.)	3	11	22
Rectosigmoid (11 to 16 cm.)	6	7	12
Sigmoid	12*	3	7
Colon	6	9	9
Other carcinoma	4	2	1
Broders' classification			
I	2	1	0
II	7	13	23
III	4	10	15
IV	1	0	0
Lymph-node metastasis			
Yes	10	10	26
No	4	14	20
None found	8	5	6

*Eleven of 12 had either peritoneal or serosal implants or liver metastasis.

Finally even if this were not a preliminary report, the prognosticating value of this cytologic examination must be very limited, by virtue of the primitive technologic method employed and the countless variables involved. If will be of particular interest, however, to ascertain the fate in 5 years of those patients who had positive or suspicious smears despite negative evidence of gross intra-abdominal metastasis. There were 35 of these patients.

This modest study does show, therefore, that tumor cells, be they dead or alive, do exist free in the abdominal cavity of patients with carcinoma of the

colon and rectum, and presumably in other forms of intra-abdominal cancers, prior to operative manipulation. Their significance is left up to the individual interpretation.

SUMMARY AND CONCLUSIONS

1. Simple cytologic smears have been taken from the cul-de-sac on almost 180 colorectal carcinomas at the beginning of the operation. These were stained and read in the usual fashion.

2. Results were: smears presumably positive for cancer cells, 33 (19 per cent); smears presumably suspicious for cancer cells, 40 (22 per cent); smears presumably negative for cancer cells, 60 (33 per cent); and smears technologically inadequate for diagnosis, 47 (26 per cent).

3. These results are correlated with operative and pathologic findings.

For their cooperation in the preparation of this study, I am indebted to Dr. Michael R. Deddish and his staff on the Rectum and Colon Service of the Memorial Center. Special thanks are in particular due Drs. William D. Johnson, John Berg, and Thomas Simon, all members of the Pathology and Cytology Departments at Memorial Center.

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EXPERIENCES IN THE SURGICAL MANAGEMENT OF TIC DOULOUREUX

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THIS paper deals with 25 years' experience in the surgical management of tic douloureux, based upon 348 patients on whom 391 operations were performed. In it are discussed the incidence, diagnosis, surgical management, complications, and results involved in these cases.

MATERIAL

The ages of the patients ranged from 26 to 90 years, with 80 per cent of them over 50 and 43 per cent over 60. The ratio of males to females was 6:7, respectively. Eighty-three per cent had symptoms for more than one year, and 40 per cent had symptoms for more than 5 years. Definite trigger mechanisms were recorded in two-thirds of the patients. Bilateral tic was present in 15. The distribution of areas involved with pain is shown in Table I.

Table I

1st division	29	2nd & 3rd divisions	120
1st & 2nd divisions	50	3rd division	52
2nd division	57	All divisions	40

Table II shows the type of procedure and the number of times the various operations were done in this series.

Table II

Rhizotomies 276	Repeat rhizotomies 9
Supraorbital avlusion 28; later rhizotomy 11	
Decompression 62 (bilateral 3)	
Decompression after rhizotomy 3	
Rhizotomy after decompression 10	
Posterior fossa 11	Tractotomy 4

DIAGNOSIS

Usually, the diagnosis of tic douloureux is rather simple—the sudden, sharp, shooting pains involving the second or third division of the trigeminal distribution on the face, associated in some cases with trigger zones on the

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face or in the mouth, are well known. Occasionally, there may be some difficulty in the diagnosis of the neuralgia involving the first division of the trigeminal nerve. In this instance, the pain is less apt to be sudden, sharp, and shooting in character but does involve the forehead area in the distribution of the supraorbital and supratrochlear nerves, with aching and in some cases burning, and with no evidence of trigger mechanisms in most cases. Our experience has been that the supraorbital nerve is frequently hypersensitive and that its palpation often initiates the pain.

It should, of course, be emphasized that trigeminal neuralgia is not associated with neurologic deficits in the distribution of the fifth cranial nerve. When such deficits are shown to be present (anesthesia of the cornea, anesthesia or hypesthesia of portions of the face, or masseter paralysis), then a paratrigeminal mass, either a tumor or aneurysm, should be suspected.

SURGICAL MANAGEMENT

The surgical treatment of trigeminal neuralgia has been fairly well standardized. Patients experiencing the first attack of the disease are usually treated conservatively. There may follow weeks, months, or even years of freedom from pain. Others may give a history of an occasional pain in the face, occurring for a few days every year or two. These patients may prefer conservative management also. Still others have repeated attacks of pain with the usual typical trigger zones, and their condition becomes worse in time. They are candidates for surgical management. In a few instances, alcohol injection after blocking of the involved division with Xylocaine may be profitable. However, injection of alcohol into the various branches of the trigeminal nerve is becoming less and less popular with the advent of effective surgical management.

Total or subtotal section of the sensory root by the temporal approach, decompression of the sensory root and ganglion,[11] section of the sensory root in the posterior fossa, medullary tractotomy, and avlusion of nerves of the face are the methods used in surgical management.

With repeated bouts of pain, decompression may be used with good results expected in 75 to 80 per cent of the patients. With recurrence of pain, the root may be partially or completely sectioned as needed. Among the very old patients, section of the sensory root may be a better initial procedure. Partial section should be preferred over complete section if section of the root is decided upon. If the patient has had alcohol injections with the last injection unsuccessful, section of the sensory root is preferred.

Decompression is practiced by us in many cases of trigeminal neuralgia, and up to this writing there has been return of pain in 17 per cent of the cases, necessitating section of the sensory root. We employ a technique which is shown in Fig. 1. After exposing the foramen spinosum, plugging it, and cutting the middle meningeal artery, the dural lining is incised along its attachment to the middle fossa and anterior petrous bone. On retraction of the temporal lobe with Cottonoid and a lighted retractor, the third division, the ganglion, and the root may now be palpated in Meckel's cave with bayonet

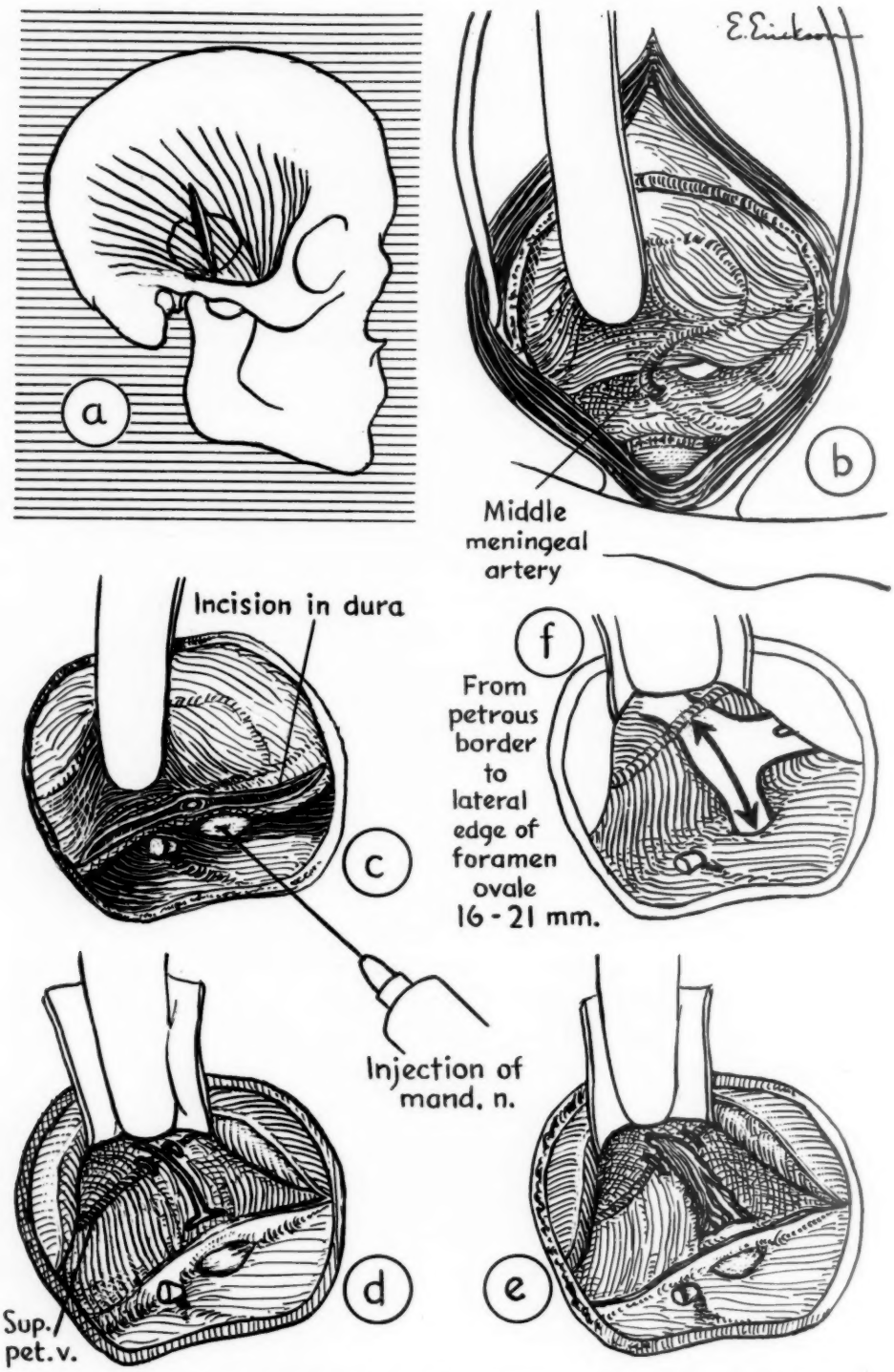


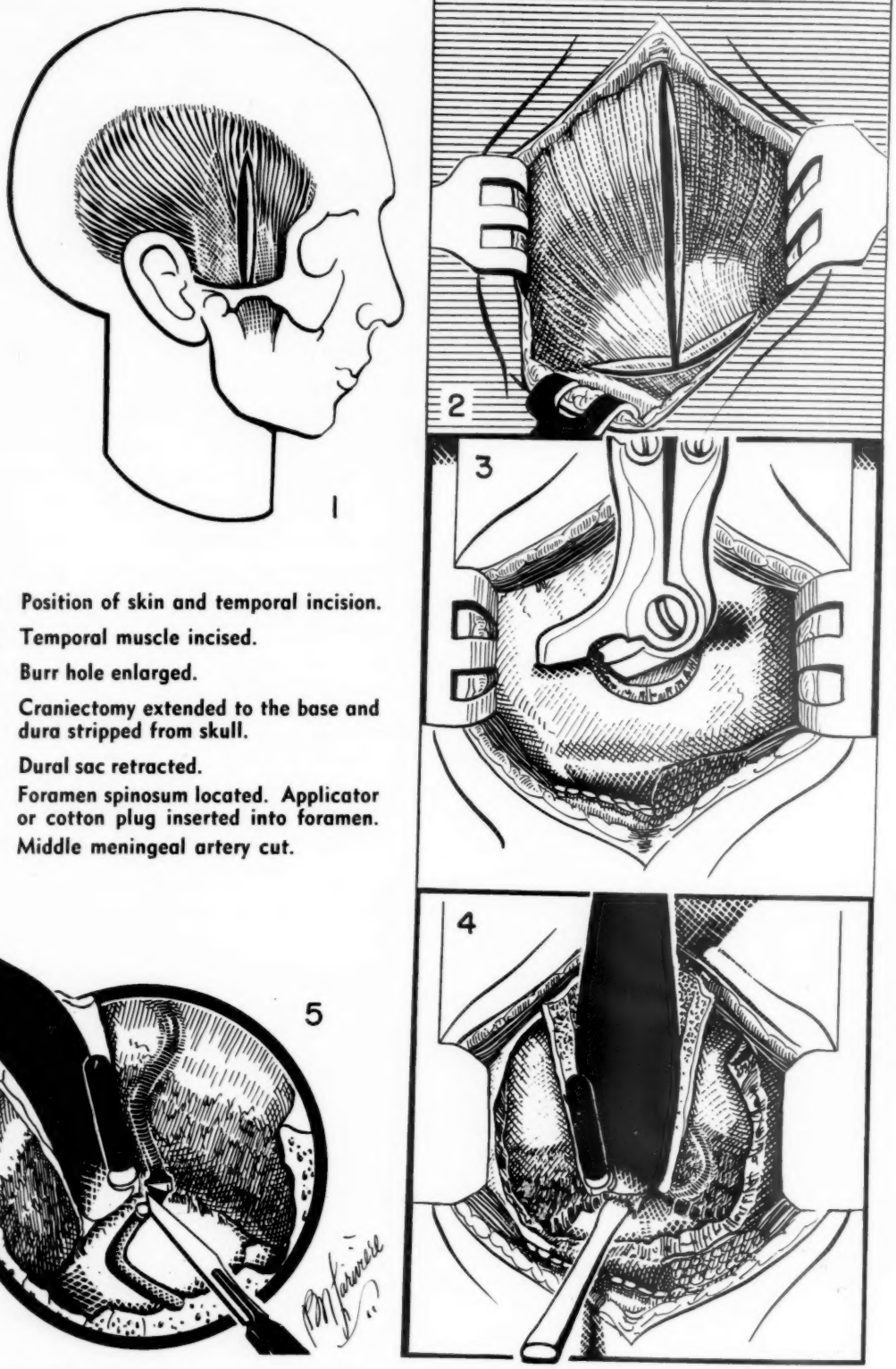
Fig. 1.—Technique of decompression of the trigeminal ganglion and root. After exposing the third division and injecting it with Xylocaine, the dura is cut and the intradural space entered. A rectangular piece of dura is removed from over the root and ganglion. The section is extended to the superior border of the petrous bone.

forceps. A rectangular piece of dura is excised from over the ganglion and the root, thus bringing into view the root fibers. The section of the dura is extended toward the brain stem until the superior border of the petrous bone is reached. In about two-thirds of the cases, clips are applied to stop bleeding from the superior petrosal sinus; in about one-third of the cases no vein appears, and presumably in these instances the superior petrosal vein traverses under the ganglion. We like to have the area well exposed so that if there is a recurrence, a re-exposure of the area is quite simple, and visualization of the ganglion and root is easily accomplished. In many of the cases where re-exploration has been resorted to, the dura has been found to be open near the ganglion with some arachnoid-like membrane holding back the cerebrospinal fluid.

Since, in the greatest number of cases, trigeminal neuralgia involves the lower divisions of the trigeminal distribution, if section of the root is decided, it is preferable to do a subtotal section to preserve the corneal and conjunctival sensations. This can be done with little difficulty in most instances. Following such a procedure, there is usually some contraction of the sensory loss, but the region of the lower and upper lips and the side of the nose usually remains anesthetic to pain and light touch for many years. It has been shown by Kahn and others that in those instances where the section involves the second and third divisions with the first division intact, there may be an anesthesia of the conjunctival lining and cornea, involving the lower half of the eye with no anesthesia in the upper half of the anterior eyeball.

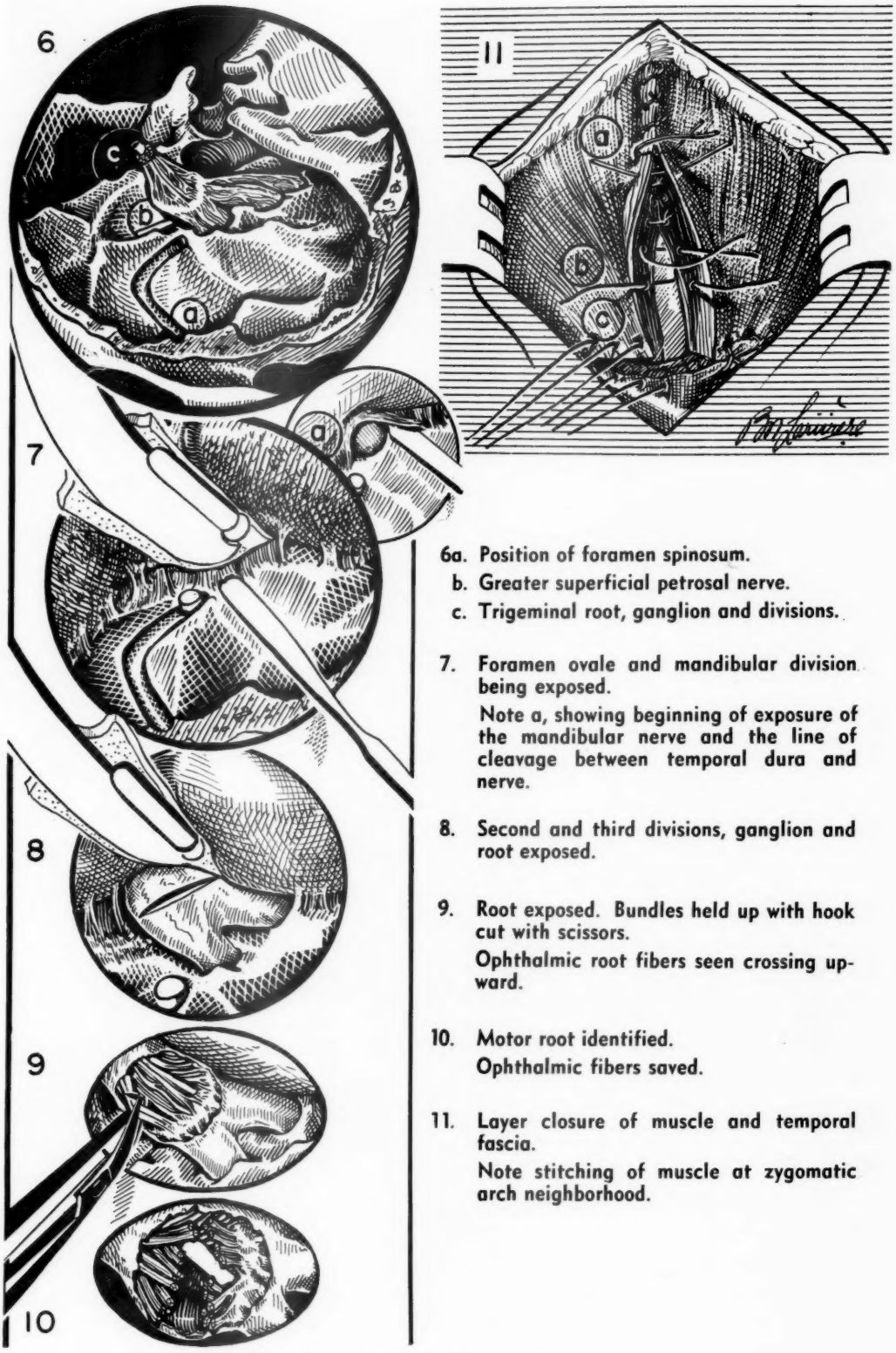
Medullary tractotomy for major trigeminal neuralgia has not been used in this series very many times. We have been afraid to use tractotomy for the reason that in many instances the third division is involved and tractotomy is more effective for first and second division pain, and the results are not constant for third division pain. We have used tractotomy, however, in those instances in which there was also need for section of the ninth and upper three cervical posterior roots for unilateral pain in malignancy of the upper neck and throat. In two instances tractotomy was used for the second side in bilateral tic with good results.

Bilateral tic douloureux was seen in 15 cases. In all of these cases except one, the condition was first present on one side, and several years later it began in the opposite side. In only one instance was there typical pain simultaneously on both sides of the face. In this particular patient a decompression was performed first on one side and several days later on the other side with apparent stoppage of the pain. In another instance a decompression was performed on the second side, but this did not stop the pain and the root was then sectioned 3 months later with an excellent result. It is rather interesting to note that these people with bilateral root section are able to carry on quite well following surgery, although a certain degree of re-education before a mirror is necessary for them to manage their eating and drinking satisfactorily. The importance of saving the motor root in these cases cannot be overemphasized.



1. Position of skin and temporal incision.
2. Temporal muscle incised.
3. Burr hole enlarged.
4. Craniectomy extended to the base and dura stripped from skull.
5. Dural sac retracted.
   Foramen spinosum located. Applicator or cotton plug inserted into foramen.
   Middle meningeal artery cut.

Fig. 2.—Technique of section of sensory root. (From Gurdjian, E. S., and Webster, J. E.: Operative Neurosurgery, Baltimore, 1952, Williams & Wilkins Co.)



6a. Position of foramen spinosum.
b. Greater superficial petrosal nerve.
c. Trigeminal root, ganglion and divisions.

7. Foramen ovale and mandibular division being exposed.
Note a, showing beginning of exposure of the mandibular nerve and the line of cleavage between temporal dura and nerve.

8. Second and third divisions, ganglion and root exposed.

9. Root exposed. Bundles held up with hook cut with scissors.
Ophthalmic root fibers seen crossing upward.

10. Motor root identified.
Ophthalmic fibers saved.

11. Layer closure of muscle and temporal fascia.
Note stitching of muscle at zygomatic arch neighborhood.

Fig. 3.—*For legend, see opposite page.*

First division neuralgia has been treated by avulsion of the supraorbital and supratrochlear nerves after a therapeutic test with local infiltration. Many cases improve with this procedure and stay well for 1 to 5 years. In many instances the return of pain is treated by complete section of the root. In 2 cases, decompression for recurrent pain after nerve avlusion gave excellent relief.

RESULTS AND COMPLICATIONS

Numbness involving one or two of the divisions of the trigeminal nerve may be present following a decompression operation in which the operator is fairly sure that no gross damage was done to the fibers of the ganglion and the root. A facial paralysis may occur following this procedure and in some cases may be seen not immediately after the operation, but 2 to 4 weeks later. Presumably this may be due to trauma to the greater superficial petrosal nerve with traction upon the geniculate ganglion and the facial nerve in the facial canal.

Fig. 4.

Fig. 5.

Fig. 4.—Bilateral tic douloureux. The left side has just been denervated. The right side had been done 8 years earlier by Dr. Max Peet.

Fig. 5.—Ulceration of the nasal border on the denervated side. Condition improved by restricting patient from rubbing nose.

With recurrence of pain among those with a partial section of the root, reoperation may employ either an intradural opening or an extradural dissection. Intradural dissection[12] may be somewhat easier if the nerve had been partially sectioned extradurally before. We have used this method on several occasions with excellent results. The dural lining over the cave is incised after opening the dura along the attached border to the middle fossa-petrous junction.

Ulcerating sores of the face were noted in two instances. We were fairly certain that these patients rubbed their faces and the sides of their noses almost constantly because of paresthesias in the area of denervation. After external irritation of the area was controlled, under hospital supervision, the ulcers healed. It has not been necessary in our cases to do a cervical sympathectomy as suggested by Dott.[1]

Fig. 6.—Carotid artery occlusion in a case with right hemiplegia following a repeat rhizotomy. The middle cerebral artery distribution is contributed to by the external carotid via the ophthalmic artery.

Peripheral facial paralysis is ordinarily seen soon after the operation. Occasionally it may become manifest 2 to 4 weeks after surgery, particularly among those undergoing the decompression procedure. In one instance the facial paralysis was due to local injection below the zygomatic arch involving the pes anserinus. This patient's paralysis disappeared within a few hours. In a few instances the paralysis may last for a week to 10 days. More frequently it lasts for 2 to 6 months. The longer the paralysis lasts the less likely is normal return of function. Mass movements of the face and facial spasms are common in the group with imperfect return of motor function. When facial paralysis is seen after total section, lateral tarsorrhaphy is a good procedure to protect the cornea.

Among these patients, operative morbidity and mortality frequently result from cerebrovascular disease. Of 8 such cases, one patient was found to have an intracranial thrombosis of the internal carotid artery. It was felt that the surgery necessary to denervate her face (third operation) precipitated the thrombosis.

The problem of corneal ulcers is an important one, but in patients who have had decompression or partial section of the sensory root this condition, of course, becomes much less likely. In the presence of a corneal ulcer, in those instances where complete section of the sensory root has been done, tarsorrhaphy is an excellent procedure. Protective eye covering is not used in our clinic on patients who have had partial section of the sensory root, and, for those who have had a complete section, the need for this protection has not been urgent, particularly if the patient wears glasses.

Postoperative paresthesias of the face are common among these patients, but only occasionally are they severe or lasting. When they are severe, the patients complain bitterly, and management is difficult and frequently unsuccessful. Among those with partial section, paresthesias are less severe and more bearable.

Complete ophthalmoplegia was present in 2 cases with recovery in both. Third nerve paralysis was seen in 4 cases with recovery and sixth nerve paralysis in one. Temporary paralysis of the fourth nerve was seen in one patient following a decompression operation.

Table III shows the numbers of the various complications encountered in this series.

TABLE III

Cerebrovascular disease	8 (5 deaths)	Diplopia	8
Hemorrhage (postop.)	3 (1 death)	Nose ulcers	2
Acute pancreatitis	1 (death)	Facial paralysis	16
Pulmonary infarction	1 (death)	Keratitis	6

SUMMARY

Surgical experiences with 348 patients with tic douloureux are presented. Statistics regarding age and sex incidence, distribution of pain, and numbers and types of surgical procedures done are given. The surgical management, results, and operative morbidity and mortality are discussed.

In general, although conservative treatment may be used in early cases, ultimately, in many, surgical treatment becomes necessary. Decompression of the sensory root has been a satisfactory first step in management in 83 per cent of patients. Those having a recurrence of the pain may then be treated by subtotal section of the sensory root. Thus in most patients now the pain is not exchanged for a numb face.

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OBSERVATIONS OF THE FUNCTION OF THE LIVER IN EXPERIMENTAL TRAUMATIC SHOCK

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THE role of the liver in the total body response to traumatic shock has long been an intriguing problem. Many investigations, previously published, have noted alteration in blood levels and hepatic clearances of various metabolites. However, the multitude of conflicting interpretations based upon animal experimentation indicates that our understanding of this problem is yet incomplete.

Most reports have noted in traumatic or hemorrhagic shock that there are several frequently encountered metabolic alterations. The blood glucose immediately rises[7, 21, 36, 51] as a response to epinephrine stimulation[12, 54, 59] and is associated with a decrease in the reservoir of hepatic glycogen.[21, 28, 36] Blood and hepatic cellular lactic acid increases and the lactate/pyruvate ratio rises.[7, 12, 51, 59] However, distortion in carbohydrate metabolism is not believed to be a primary factor in the pathogenesis of shock since the same type of alteration occurs whether the liver is oxygenated or not.[51] The traumatized tissues utilize glucose at a faster rate than do the normal tissues.[53] The hepatic stores of high energy phosphate compounds decrease rapidly in shock,[28, 41] but the decrease seems unrelated to the lethality of the preparation. The amino acid content of the peripheral blood, as well as of the hepatic cells, rises; the degree of increase reflects the severity of shock.[12, 26, 44, 46] This increase is due to an increased tissue release of amino acid[43] and, because of decreased hepatic blood flow, a decrease in hepatic clearance of amino acids.[12, 26] Fibrinogen and prothrombin levels of the plasma decrease after trauma.[15, 16] Bilirubin formation and excretion do not depend upon the integrity of hepatic arterial flow and can proceed in the hypoxemic liver.[56] Blood ammonia, implicated as a factor causing coma in clinical hepatic failure[33, 57] has not been shown to rise to toxic levels in experimental shock.[11, 35, 60] Hepatic blood flow decreases during shock and the resistance of the portal bed rises.[18, 58]

The relationship of bacterial activity to the effects observed in traumatic or hemorrhagic shock has also been subject to recent debate. Antibiotic therapy has been reported to increase the resistance to hemorrhagic shock

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in the dog.[13] Clearance of intravenously injected *Escherichia coli* from the blood of shocked dogs decreases,[13] sensitivity to endotoxin increases,[48] and the plasma level of properdin as well as phagocytosis-promoting factors decrease.[14, 49] However, much of this data has not been confirmed so that this question remains open.[9, 22, 45] In Korean battle casualties, Balch[1] noted only slight impairment in the phagocytic activity of the circulating neutrophils in several patients. The capacity to synthesize specific antibodies, and the plasma complement level were unchanged. Because the Kupffer cells of the liver are a primary filter center for blood-borne bacteria, the use of reticuloendothelial blockade has been a useful tool in studying the relation of shock and bacterial resistance. Colloidal thorium dioxide, in sufficient doses, has been shown to interfere with removal of bacteria from the circulating blood,[32] increase sensitivity to injected endotoxin,[2, 20, 55] and decrease resistance of rats to drum shock.[34]

A recently developed preparation for evaluating the effects of a standardized lethal trauma has been under investigation in these laboratories for several years. It involves creation of massive soft tissue injury in both hind extremities of Texas angora goats by detonation of small charges of a high explosive.[37] In reporting the influence of various therapeutic programs on prolongation of survival time, Mansberger[31] noted that systemic penicillin therapy would increase the mean survival time of the animals from 19 to 55 hours. Oppenheimer[38] recorded changes in the quantitative bacterial flora of the wounds and found significant depression in the gram-positive organisms in penicillin-treated animals. The alteration in plasma electrolytes and nitrogenous fractions has already been reported by Gillette.[19] Because of interest in the response of the various activities of the liver to traumatic shock, several broad studies, herein reported, were undertaken. In this study, we observed several major changes in liver function in the untreated animals as well as penicillin-treated animals, to see if the prolongation in survival would be reflected in the indices employed.

METHODS

Texas Angora goats weighing between 30 and 40 Kg. were used throughout this study. The animals were castrated at less than 6 months of age and were 5 to 8 years of age when used experimentally. These investigations were carried out in the summer and autumn of the year during which time the animals were maintained on a hay-grain diet. Injury was created under pentobarbital sodium anesthesia (10 to 12 mg. per kilogram of body weight) by detonation of small charges of tetryl, a high explosive, on carefully predetermined sites on the hind extremities. The major vessels bleeding at the wound site were clamped immediately after injury, and a clean but unsterile dressing was loosely applied. The animals were then observed in a restrained prone position on a cart in a room maintained at 22° C. Samples of blood were obtained from the jugular vein periodically, and the exact volume of the removed samples was replaced by transfusion of normal goat blood.

Serial determinations were made on four groups of animals, 10 animals in each group. Group A consisted of animals undergoing standard injury, without any specific therapy. Samples were analyzed immediately before blast, 2 hours after blast (to allow recovery from anesthesia), and every 4 or 5 hours until death. The mean survival time

of the animals in this group was 19.4 ± 5.3 hours (standard deviation). Group B served as control for A; the animals were restrained on carts for a period comparable to the average survival of the injured group. Samples were taken at the same times in the day as in the wounded group to consider diurnal variation. Group C consisted of injured animals given penicillin therapy. Each animal received 300,000 units of procaine penicillin G and 1,000,000 units of crystalline penicillin G potassium one hour before injury, immediately after injury, and every 8 hours thereafter. The mean survival time for this group was 38.4 ± 10.1 hours. Samples were analyzed immediately before blast, 2 hours after blast, and every 8 hours until death. In order to assess the relationship of liver function to longer survival, this group of 10 animals was composed of those having survival times of greater than 23 hours. A few penicillin-treated animals had survivals of less than this time and were not included. Group D consisted of 10 animals serving as controls for the longer-term survivals. These were also given the same penicillin regimen and samples at the same times of the day as in Group C. The animals in Group D were maintained on carts for a total of 69 hours. All animals were offered water periodically but no food. Because of the capacious gastric complex in this species (10 to 15 per cent of body weight with contents), lack of food for several days probably had no effect on any of the determinations under consideration in this report. The two uninjured control groups were not given pentobarbital anesthesia. The animal preparation represents marked uniformity with respect to the size of the wound and its resultant physiologic effects.

In all the foregoing groups, liver samples were taken at the time of death for microscopic study. The specimens were fixed in formalin, and sections were stained with hematoxylin and eosin, with oil red 0 to evaluate the amount and distribution of lipids, and with periodic acid-Schiff reagent to stain glycogen.

Four parameters of liver function were used to assess the effect of the trauma upon the liver. (1) Bromsulphalein* excretion was used as an index of liver blood flow. A modification of the Rosenthal and White technique was used.[42] It was found that the excretory power of the liver in goats was greater than in man, so that a larger dose of dye had to be used. Accordingly the test as standardized for our preparation consisted of rapid injection of 5 mg. of the dye per kilogram and sampling from the jugular vein opposite the site of injection 30 minutes later. The coefficient of variation in 15 determinations of a particular sample was 8.4 per cent. (2) Blood ammonia was determined by the method of Seligson and Seligson[52] as modified by Bessman.[3] The coefficient of variation for repeated determinations was 15.3 per cent. (3) Blood glucose was determined by the method of Kingsley and Reinhold,[25] a colorimetric measure of the true glucose present in the blood. The coefficient of variation was found to be 3.1 per cent. (4) Direct and total bilirubin in the blood was determined by the method of Malloy and Evelyn[30] as modified by Ducci and Watson.[10] The coefficient of variation in repeated determinations of the direct bilirubin in the same sample was 7.7 per cent and that of the total bilirubin was 9.1 per cent.

The changes which were observed in the several parameters of liver function were found to be more closely related to approaching death than to the time elapsed between injury and the particular observation. Therefore observations were recorded as having taken place at a certain percentage of the total survival time of the animal under consideration. To obtain a smooth curve that could be considered as representative to the results from a group of animals, a graphic approach was utilized which is based upon the method of advancing moments.[24] To establish the adequacy of this approach the 0 per cent (preblast), 20, 40, 60, 80, 87.5, and 100 per cent (penicillin-treated, only) points of total survival time were examined and residual variances computed for these points.

To evaluate the effect of reticuloendothelial blockade on survival after shock, a stabilized suspension of 24 to 26 per cent thorium dioxide† was used. Immediately after

*Sulfobromophthalein sodium obtained from Hynson, Westcott and Dunning, Inc., Baltimore, Md.

†Thorotrast obtained from Testagar & Company, Inc., Detroit, Mich.

injury 25 c.c. was injected intravenously, and the dose repeated every 4 hours until 100 c.c. total dose had been given (provided the animal survived for the necessary 12-hour period). Preliminary testing showed this dose to be tolerated by the uninjured animal.

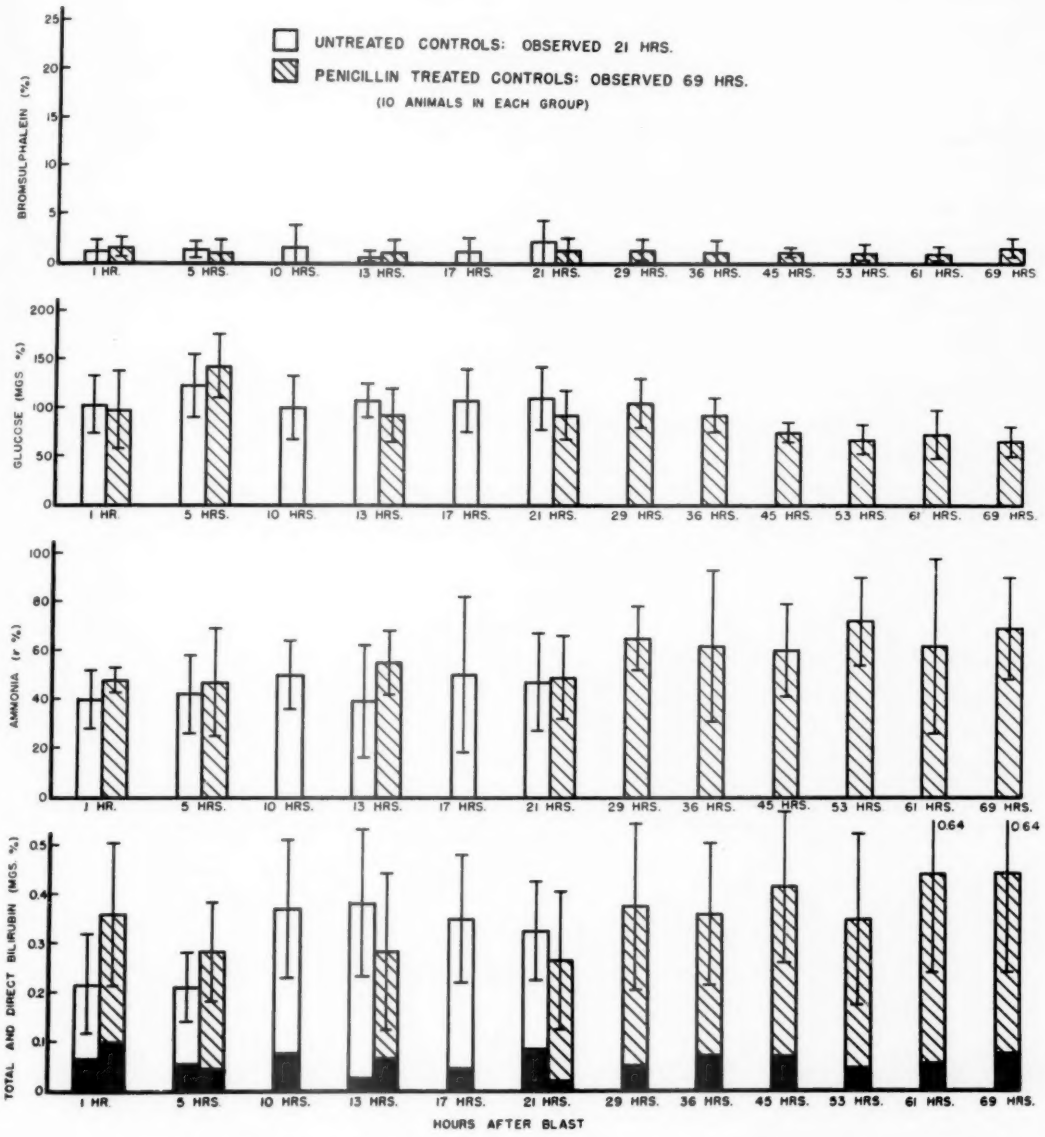

Fig. 1.—Liver studies in control animals. Mean serial determinants. Changes in 10 untreated control and 10 pencillin-treated control animals. The vertical bars represent standard deviation.

RESULTS

Serial Studies.—It was found that changes in function resulted from the position on the cart. Therefore, these must be considered first. Fig. 1 summarizes the mean results obtained from the untreated control group of 10 animals and from the penicillin-treated control group of 10 animals. The vertical bars represent standard deviation. It will be noted that the untreated

group had observations repeated at approximately 4-hour intervals over a 21-hour period. The duration of observation corresponded with the mean survival of the untreated wounded animals which was 19.4 ± 5.3 hours. The controls for the evaluation of penicillin therapy were followed for a total of 69 hours, a much longer time than absolutely necessary since the mean survival of the penicillin-treated wounded animals was 38.4 ± 10.1 hours.

The Bromsulphalein retention remained quite constant in both groups of controls. The mean retention during all periods of observation usually was 1 to 2 per cent. The jugular venous ammonia level averaged initially 40 ± 12 γ per cent in the untreated controls. Over the first 21 hours, no significant changes in this level were noted, but in the longer period of observation used for the penicillin-treated group of controls, there was a rise in the mean level to a terminal 69 ± 21 γ per cent ($P < 0.05$).

The glucose level in 9 unexcited, standing goats ranged from 60 to 76 mg. per cent with a mean of 72 mg. per cent. One hour after being placed on carts, there was obtained a mean of 102 ± 30 mg. per cent in the untreated controls, and 97 ± 40 mg. per cent in the penicillin-treated controls. Five hours after being placed on the cart, the average in both groups rose appreciably, reaching means of 123 ± 32 mg. per cent ($P < 0.2$) in the untreated controls and 142 ± 33 mg. per cent in the penicillin-treated controls ($P < 0.05$). The exact mechanism of this rise is not known. From this time on there was a progressive decline in the glucose level in the blood. After being on the cart for a total of 69 hours, the penicillin-treated controls had a mean value of 65 ± 15 mg. per cent. The total bilirubin fluctuated considerably in both groups of control animals. Initially there was 0.22 ± 0.10 mg. per cent in the untreated and 0.43 ± 0.17 mg. per cent in the penicillin-treated group. In general there was a slight rise in the mean level after the first 21 hours but the standard deviation was great. The terminal level of the penicillin-treated group was 0.44 ± 0.20 mg. per cent. The direct-reacting bilirubin fraction did not change appreciably in either control group and at no time had a mean value of greater than 0.10 mg. per cent.

Turning to the results in the untreated wounded animals (Fig. 2), there will be noted a progressive rise in Bromsulphalein retention after injury to a mean value of 12.2 ± 9.8 per cent after 87.5 per cent of the survival time had passed ($P < 0.001$). The venous ammonia increased from an initial value of 34 ± 11 γ per cent to a level of 73 ± 31 γ per cent after 87.5 per cent of the survival time had passed ($P < 0.001$). The blood glucose followed the same pattern as noted in the control animals. The total bilirubin did not change appreciably nor did the direct-reacting fraction increase significantly.

The penicillin-treated wounded animals had a mean survival of approximately twice the untreated wounded (38.4 ± 10.1 hours). In this group hepatic blood flow as measured by Bromsulphalein retention decreased progressively throughout the postinjury observation period. The mean terminal Bromsulphalein retention was 24.0 ± 19.8 per cent ($P < 0.01$). The venous ammonia increased moderately from an initial 53 ± 23 γ per cent to a terminal

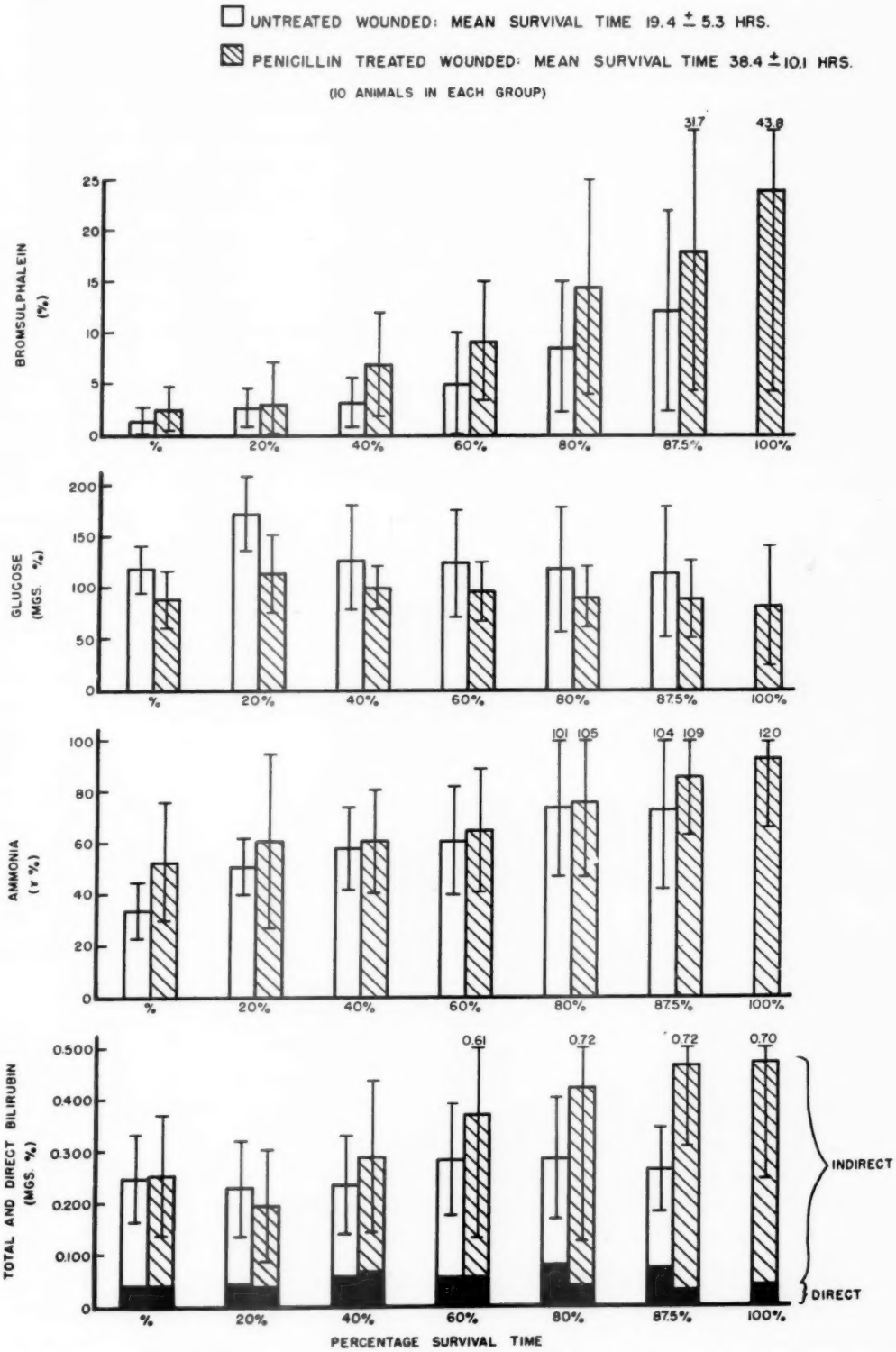

Fig. 2.—Liver changes in wounded animals. Mean serial determinant. Changes in 10 untreated wounded and 10 penicillin-treated wounded animals. The vertical bars represent standard deviation.

93 ± 27 γ per cent ($P < 0.01$). The blood glucose followed the same pattern as in the penicillin-treated controls. The total bilirubin increased from an initial 0.25 ± 0.12 mg. per cent to a terminal 0.47 ± 0.23 mg. per cent. As noted on Fig. 3, this increase in bilirubin was a result of increase in the indirect-reacting fraction, since no appreciable change occurred in the direct-reacting component. When compared with the changes in the penicillin-treated controls (Fig. 2) the changes in bilirubin do not appear significant in the wounded animals.

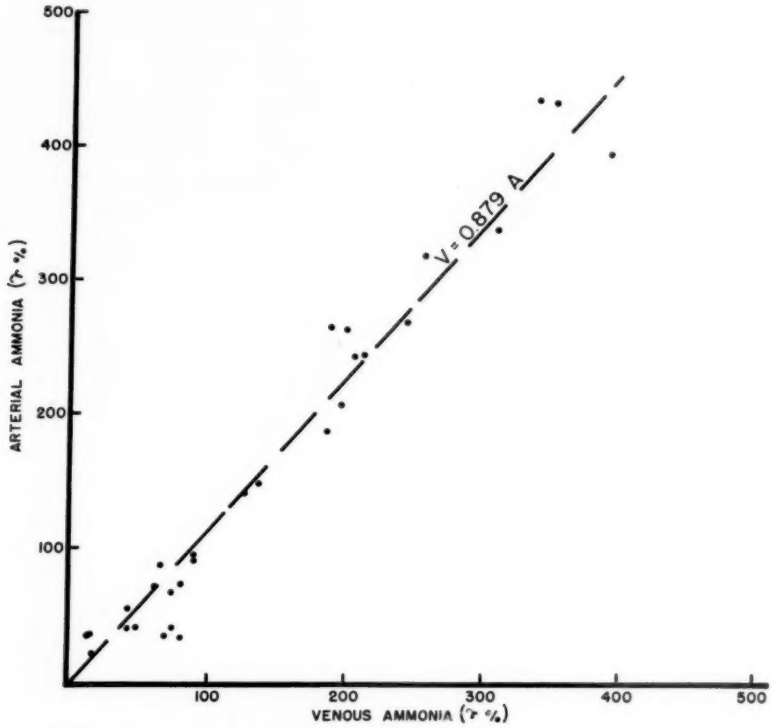

Fig. 3.—Response to intravenous infusion of ammonium chloride (3 animals). Regression line obtained by method of least squares showing relation between arterial and venous ammonia content.

In certain of the histologic sections from the longer survivals, there was a variable amount of periportal and central lobular congestion with early central lobular cell degeneration. The amount of glycogen observed in the hepatic cord cells with the periodic acid-Schiff reagent stain was within normal limits as compared with the nonwounded goats.

Fat staining with oil red 0 revealed considerable quantities of finely particulate lipid in most of the cases, tending to fall, however, within normal limits. No major histopathologic change was observed in most of the sections of the liver that were examined.

Ammonia Infusion Curve.—Bessman[3] has pointed out that the arterial level of ammonia is about 20 per cent greater than the jugular venous ammonia in man and more accurately reflects the symptoms associated with ammonia intoxication. In order to help in interpretation of data obtained in our

studies based upon jugular venous blood, we obtained arterial and jugular venous levels simultaneously over a wide range of values by artificially raising the blood level with an infusion of ammonium chloride.

Three animals were used to determine simultaneous arterial and jugular venous ammonia concentrations. Polyethelene catheters were placed in the jugular vein, inferior vena cava, and brachial artery. After control samples were obtained, ammonium chloride (1 mg. NH_3 per milliliter) was introduced into the inferior vena cava. The rate of infusion was controlled with a finger pump and gradually increased over the next 3 hours from an initial rate of 0.5 ml. per minute to a final rate of 14.5 ml. per minute. During the course of the infusion, 8 simultaneous arterial and venous samples were drawn from each animal.

Fig. 3 shows the results of this series. By the method of least squares, a straight line drawn between the multiple points shows the venous blood to have 87.9 per cent of the ammonia level of the arterial blood. At the lower levels there was some scatter, presumably because of limitations in the method used. It appears that sampling of the jugular venous blood provides a good index of the arterial ammonia level in normal controls. Furthermore, the calculated arteriovenous difference in the goat (12 per cent) is comparable to that in man (20 per cent) when allowing for the smaller weight of the brain.

Blood Ammonia 18 Hours After Injury.—The level of ammonia in blood from various sources was investigated in two groups of injured animals and compared with uninjured controls. Eighteen hours after blast, the 3 animals in each group were anesthetized with sodium pentobarbital, then turned on their backs. Through a midline abdominal incision, samples of blood were obtained from 4 abdominal vessels. Samples were also obtained from the jugular vein for comparison. Each sample was run in duplicate. Table I shows the results of this study. The figures represent the average blood levels for the 3 animals used in each series.

It will be noted that the ammonia levels in the various vessels of the injured untreated and injured penicillin-treated animals are considerably higher than those in the controls. Of particular interest is the level of ammonia in the

TABLE I. AMMONIA CONTENT IN BLOOD FROM VARIOUS SOURCES IN 3 ANIMALS 18 HOURS AFTER INJURY

SOURCE OF SAMPLE	CONTROLS (3 ANIMALS) γ %	INJURED UNTREATED (3 ANIMALS) γ %	INJURED PENICILLIN-TREATED (3 ANIMALS) γ %
Jugular vein	13 (12-18)*	28 (17-36)*	31 (28-36)*
Inferior vena cava	19 (10-26)	42 (26-70)	38 (26-56)
Portal vein	267 (181-360)	346 (203-406)	415 (244-573)
Hepatic vein	20 (12-26)	46 (26-69)	53 (28-90)
Aorta	14 (12-19)	41 (26-70)	30 (12-43)

*Range.

portal vein blood, compared with the level in the hepatic vein blood. In the 3 controls the hepatic vein blood had an ammonia level of 7.5 per cent of that of the portal. The injured untreated and injured penicillin-treated had hepatic vein levels representing 13 per cent of those found in the corresponding portal veins. It would thus appear that there may be slight impairment in the metabolic function of the liver occurring in animals after a prolonged period of traumatic shock. However, the failure to find a pronounced difference in this derangement indicates that this specific liver function cannot be correlated with the much longer survival of the penicillin-treated injured animals.

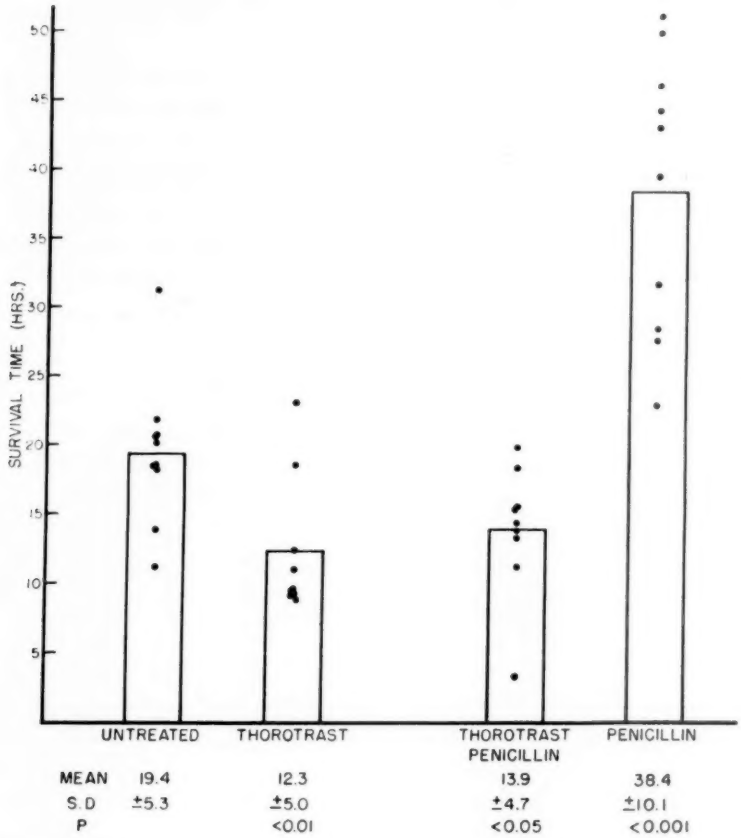

Fig. 4.—Survival time of four groups of experimental animals indicating the effects of penicillin treatment and of reticuloendothelial blockade with Thorotrast.

Survival After Reticuloendothelial Blockade.—Thorotrast was administered to saturate the phagocytic activity of the reticuloendothelial cells of the liver and spleen. The results of these experiments are summarized in Fig. 4. A total of 18 animals were used, of which 9 were given only Thorotrast. The others were given Thorotrast and penicillin. There was a significant fall in survival in both groups by comparison with injured controls. The mean survival of the animals not given antibiotics was slightly less than those given penicillin in addition to Thorotrast.

DISCUSSION

The animal preparation involved in these experiments represents a response to lethal trauma. The large area of hindleg muscle damage challenges the life of the animal in several ways. There is a major factor of reduction in circulating blood volume. In addition, there is a second stress provided by the establishment of severe infection. Penicillin has been shown to be extremely effective in reducing the latter stress by a depression of the gram-positive organisms.[38] Parenteral streptomycin was ineffective in altering survival time[31] despite depression of the gram-negative flora of the wound.[38] More recently, it has been shown that the penicillin effect is a result of depression of one group of gram-positive organisms, namely, the Clostridia, in the wound.[29]

The results of the serial studies of liver function indicate a progressive decrease in liver blood flow as measured by Bromsulphalein excretion in both the untreated and penicillin-treated animals. It appears that survival in the traumatic shock preparation under study does not depend upon maintenance of a critical rate of hepatic blood flow. It has been shown that the rate of Bromsulphalein excretion is an accurate index of liver blood flow in normal humans[4] as in other normal species. For purposes of interpretation, it has been assumed that, in the situation presented in these experiments, the Bromsulphalein excretion is equally valid as an index. The conclusion that depression in blood flow below a critical rate was not observed in the goat preparation might be contrasted with evidence that resistance of dogs to hemorrhagic shock is greatly extended by arterial perfusion of the portal blood, thereby relieving the hepatic hypoxemia.[6, 8, 17, 23] The dog liver harbors various species of Clostridia which cause massive necrosis following ligation of the hepatic artery.[5] Hepatectomy before bleeding, on the other hand, fails to change the survival time of dogs following a standard hemorrhage.[39] It may be that marked decrease in arterial pressure and the consequent reduction in oxygen tension of the livers of shocked dogs permit clostridial emergence from the normal inert status. The liver of the goat,[27] like that of man,[40, 47] is normally sterile. To support this speculation are data showing survival of dogs following hepatic artery ligation, provided appropriate antibiotic therapy is instituted.[5]

Blood levels of ammonia remain remarkably well controlled in view of the marked reduction of blood flow. There was a statistically significant increase in the mean level of the last sample obtained before death over the sample taken before injury ($P < 0.001$, untreated; $P < 0.01$, penicillin-treated). The highest value recorded in any of the injured animals was a terminal sample containing 150 γ per cent. By infusing a solution of ammonium chloride and obtaining simultaneous arterial and venous contents of ammonia over a wide range of values, the jugular venous levels were found to be a close indication of the "true" or arterial levels in the normal goat. The arterial ammonia could be thus artificially elevated to levels of 400 γ per cent in control animals without any observable ill effect. Because values approaching this

elevation were never observed in any of the wounded animals, it seems unlikely that ammonia intoxication could have occurred in the period following injury. It is not possible to rule out by these experiments, a vastly increased sensitivity to ammonia in the presence of shock but it seems highly unlikely. Further evidence that liver function, as measured by ammonia clearance, was preserved in shock was found by obtaining portal and hepatic vein samples after injury. Eighteen hours after injury, both untreated and penicillin-treated animals were found to remove more than 85 per cent of portal vein ammonia. This occurs at the same time when the untreated animals were close to expected death, while the penicillin-treated animals could have been expected to survive for at least another 24 hours. Thus there is sufficient hepatic reserve, short of the agonal stage, to remove this rather toxic metabolite from the portal blood. Eiseman[11] reached a similar conclusion in evaluating changes in ammonia in the shocked dog.

The mean blood glucose remained elevated above a level considered normal in the resting, unexcited animals throughout the survival of both the untreated and penicillin-treated groups. The range of values for blood sugar obtained from goats in their normal environment extended from 60 to 76 mg. per cent. In 5 of the animals wounded, terminal samples were obtained that might be considered hypoglycemic. These were terminal samples in all cases, having a value of less than 40 mg. per cent. Only one of the 5 animals had a terminal sample of less than 30 mg. per cent. The other 15 animals in both wounded groups all maintained normal or above-normal levels of glucose. Sections of the liver stained with periodic acid-Schiff reagent did not indicate much depletion of hepatic glycogen. The maintenance of an elevated glucose, along with histologic evidence that marked reduction in hepatic glycogen did not occur, is interpreted as showing continued synthesis. The large gastric complex in these animals (composing 10 to 15 per cent of body weight) is usually full of ingesta before injury and therefore might supply a continuous flow of nutrients. Continued absorption from the intestinal tract can only be intimated. However, it will be noted (Table I) that the ammonia levels in the portal veins of injured animals were not decreased. Therefore, products from the intestinal tract might well have been absorbed.

Bilirubin did not become significantly elevated in any of the experiments. The reduction in survival time in animals given Thorotrast to inhibit reticuloendothelial phagocytosis is interpreted as emphasizing the important function performed by this tissue in the presence of traumatic shock. A word of reservation is necessary, however, since there may be certain unknown side effects of Thorotrast, not related to reticuloendothelial system blockade, which influences survival time.

Scott and Howard[50] reported observations of certain liver function tests in severely wounded battle casualties. They noted no evidence of hepatic insufficiency but did record some deviation from the normal. In the traumatic shock preparation used for these experiments, it appears that the liver continues to function under the most adverse conditions, existing after severe trauma, as an efficient and integrated organ.

SUMMARY

1. Serial observations of Bromsulphalein excretion, blood levels of glucose, ammonia, and bilirubin were made in uninjured goats and in goats subjected to a standard lethal trauma. Wounded animals not having any specific therapy had a mean survival of 19 hours; penicillin-treated injured animals had a mean survival of 38 hours.

2. In both groups, there was a variable depression in Bromsulphalein excretion, which could not be correlated with the duration of survival following injury. It was concluded that depression below a critical rate of hepatic blood flow was not a factor influencing survival time.

3. Changes in the levels of glucose, ammonia, and bilirubin, when compared with appropriate controls, indicate that the liver continues to function effectively and efficiently in the presence of severe traumatic shock. The longer survival provided by penicillin therapy was not reflected in significant differences in the parameters of liver function used in this study.

4. Reticuloendothelial saturation with Thorotrast caused a significant reduction in survival time after injury whether or not animals were treated with penicillin. It is believed that after trauma a dependence upon functioning reticuloendothelial tissue in the liver is thereby demonstrated.

5. The relationship between the results of these experiments and the data obtained from other animal preparations as well as human studies is discussed.

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A SYSTEM FOR VENOARTERIAL PUMPING

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INTRODUCTION

IN POTENTIALLY reversible cardiac lesions such as acute myocardial infarction, massive pulmonary embolism, and some cases of congestive heart failure, mechanical support of the circulation may be beneficial. The use of an artificial heart-lung apparatus has been attempted for short periods in myocardial infarction,[6] and animal work has suggested that acute heart failure may be relieved by pumping blood from the inferior vena cava to the aorta.[1]

A closed extracorporeal system is described here which can be used to increase systemic perfusion or reduce cardiac work over a long period. Blood is drained from the superior vena cava and pumped into the aorta at the bifurcation without oxygenation.

EQUIPMENT

The apparatus† consists of a collecting chamber and a pump (Fig. 1). It is simple in design, easily portable, and can be autoclaved as a single unit. Electrical power is not required. Bardic catheters are inserted in a jugular vein and a femoral artery and are connected by nylon adapters to Tygon tubing of 3/8 inch (1 cm.) internal diameter which is used throughout the system. Two nylon adapters with side-arm stopcocks allow sampling, priming, and the removal of air. A coil of tubing may be inserted in a water bath to allow the production of hypothermia.

The collecting chamber is a thin-walled, transparent Silastic cylinder of 200 ml. capacity in a close-fitting rigid Plexiglas case suspended from a gram scale. The pump consists of a cylinder of heavy Silastic, 1/8 inch (3 mm.) thick, with a high gloss internal finish and Hufnagel-type ball valves at each end. The cylinder is 20 cm. long and has an internal diameter of 2.5 cm., with a capacity of approximately 80 ml. It is enclosed in a rigid Plexiglas case of 5 cm. internal diameter and is emptied by pulses of compressed air. A valve reduces the compressed air supply to 30 pounds per square inch, and a second

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reducing valve allows delivery of any fraction of this pressure to the pump, so controlling the stroke output. The rate of pumping may be varied from 20 to 150 per minute. A rate of 44 per minute has been found satisfactory. Compressed air is delivered to the pump casing for half of each cycle.

EXPERIMENTAL PROCEDURE

Fresh dog blood is obtained less than 2 hours before priming. Donor animals are lightly anesthetized with 250 to 300 mg. Pentothal intravenously. Blood is drawn from the terminal aorta via a cannula in the left femoral artery into collecting bottles containing 10 mg. of heparin per 500 ml. of blood and is kept in a water bath at 42° C until needed.

The subject dogs are male and female mongrels weighing between 15 and 25 Kg. They are lightly anesthetized with 300 to 500 mg. Pentothal intravenously without premedication and are secured supine on the operating table. Anesthesia is maintained with supplemental doses of 50 to 100 mg. Nembutal intravenously. An endotracheal tube is inserted and connected to a closed-circuit spirometer containing 100 per cent oxygen which allows continuous measurement of the oxygen consumption.

The animal is heparinized with an initial dose of 1.5 mg. per kilogram of body weight intravenously, supplementd by a continuous slow infusion of 1 mg. per milliliter to keep the clotting time between 30 and 45 minutes. Polyethylene tubing (PE 320) is inserted in the aorta and the superior and inferior venae cavae, and a No. 7 Cournand catheter is placed in the pulmonary artery under fluoroscopic control to obtain pressure and blood samples. Pressures are recorded with Statham P23Db strain gauges and a Sandborn Polyviso. Fluid and electrolyte balance is maintained by the intravenous route. Esophageal temperature is monitored by a Telethermometer. In bitches a catheter in the bladder allows the continuous collection of urine. Penicillin (300,000 units) and streptomycin (1 Gm.) are given intramuscularly every 12 hours.

OPERATION OF THE SYSTEM

The system is primed with 800 ml. of blood through one side-arm adapter while air escapes from the other (Fig. 1). The arterial and venous cannulae are occluded and residual air is eliminated by circulating blood through the connecting line. The collecting chamber is distended to the limits allowed by the Plexiglas case.

The connecting line is then clamped, and the cannulae opened. Blood drains into the collecting chamber under the influence of gravity and is pumped into the lower aorta. A gradient of 100 cm. is used for gravity drainage. After a period of slow pumping to allow adjustment of the circulation, flow is increased to a maximum. As long as the pump output is less than the maximum possible venous drainage, the collecting chamber remains distended and the system will operate for long periods without adjustment. The volume of blood in the extracorporeal circuit is rigidly controlled. Loss of blood from the venous system is prevented by the limited capacity of the

collecting chamber, and if venous drainage is obstructed this chamber collapses and the animal receives less than 200 ml. of additional blood. The time taken for the pump to remove 100 Gm. of blood from the collecting chamber when venous drainage is temporarily occluded is used as a measure of the extracorporeal flow. The system is stable and may be used for long periods with a minimum of supervision.

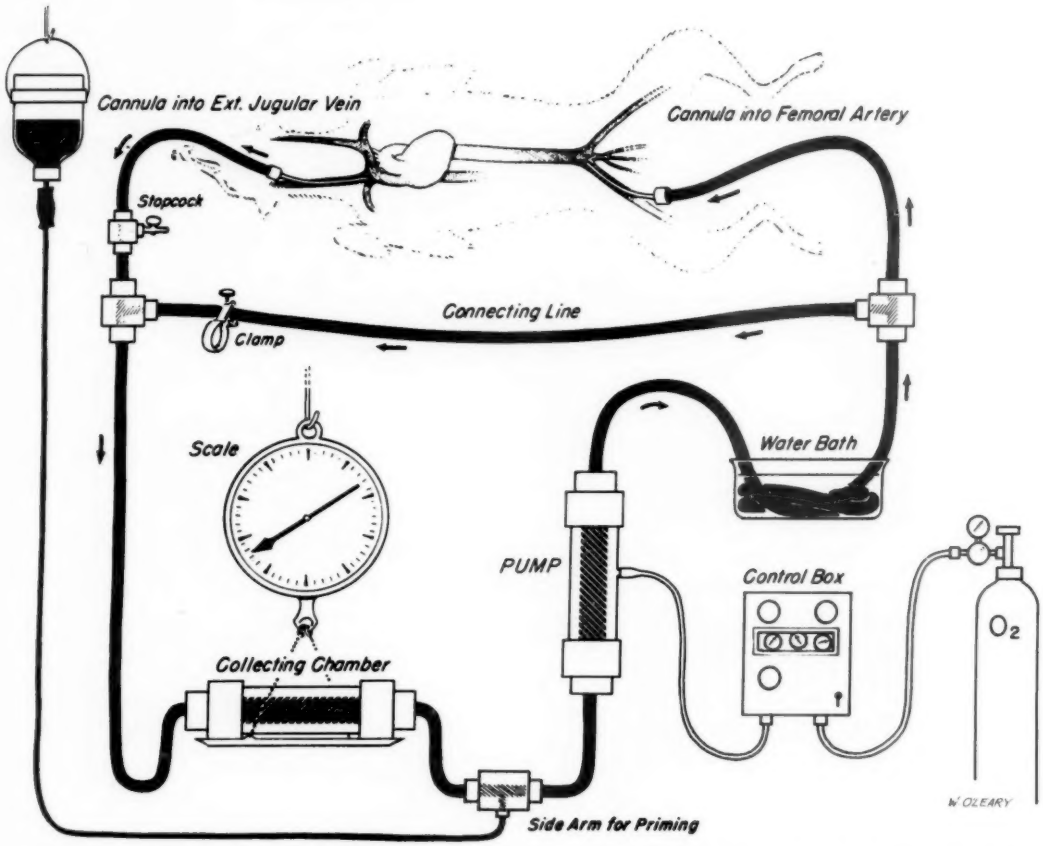

Fig. 1.—The system used for venoarterial pumping in animals. The collecting chamber is filled by gravity drainage of superior caval blood through a cannula in an external jugular vein. The pump is driven by pulses of compressed air. Blood passes through the water bath into the lower aorta via a cannula in a femoral artery. The stopcocks and connecting line are used for priming and evacuation of air.

DISCUSSION

The simplest closed system for venoarterial pumping would be an uninterrupted tube from superior vena cava to aortic bifurcation milked by a finger or roller pump. These peristaltic pumps destroy red cells and liberate hemoglobin too rapidly to permit perfusions lasting for more than a few hours.[1] In contrast the Silastic pumping chamber has caused no detectable hemolysis even after 24 to 48 hours of animal perfusion. In the only human subject, serum hemoglobin concentrations were less than 5 mg. per cent after 10 and 16 hours of pumping.

Although gentle with blood the Silastic pump exerts strong suction during its filling phase. This discontinuous suction tends to collapse the cava and

limit the volume of venous blood that may be withdrawn. The thin-walled collecting chamber eliminates direct suction on the cava, allowing steady gravity drainage. The maximal rates of flow attained without the collapsible chamber were 35 to 40 ml. per kilogram per minute. Drainage rates of 60 to 80 ml. per kilogram per minute are regularly achieved through a single superior caval cannula with the chamber in the line.

A completely closed system is essential for prolonged venoarterial pumping since a blood-air interface is a potential site for changes in the blood proteins.[5] Such a system also offers the advantage of accurate control of fluid volumes and eliminates the risk of gaseous emboli.[3] The open oxygenators in current use produce too much damage to the coagulation mechanism and the formed elements of the blood to allow their operation for prolonged periods.

The technique for venoarterial pumping without oxygenation described here differs from that used by Connolly and associates[3] in that the lower part of the body is perfused with relatively well-oxygenated blood from the superior caval system. Circulating blood from the inferior cava to the lower aorta without oxygenation will produce progressive desaturation and hypoxia of the lower limbs and trunk. This is avoided in the present system.

Experimental studies in animals[4] have shown that venoarterial pumping at rates of 40 to 80 ml. per kilogram per minute can be maintained for up to 52 hours with survival. The oxygen of blood supplying the vital organs is not significantly affected, and blood pressure, renal function, coagulation, electrolyte, and acid-base patterns show no major disturbance.

The system contains built-in safeguards against overperfusion and uncontrolled blood loss and seems suitable for prolonged venoarterial pumping in man. It has been used in one patient for 26 hours without ill effect.

SUMMARY

A closed system for venoarterial pumping without oxygenation is presented. The system is stable and nontraumatic and is suitable for prolonged use. The technique used in animal work is described. Venoarterial pumping has been performed for 52 hours in dogs with subsequent survival and for 26 hours in man.

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ANTIFIBRILLATORY AGENTS AND SURGERY TESTED BY CLOSED CHEST CORONARY OCCLUSION IN THE PIG

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MOST of the experimental work on the subject of coronary artery ligation including the testing of medications, antifibrillatory drugs, and surgical procedures has been done on dogs. Although varied and conflicting results do not necessarily invalidate any given set of data, considerable difficulty and indecisiveness exist in the over-all interpretation.[3]

In a previous report,[4] factors influencing the seemingly simple procedure of coronary artery ligation were outlined, and a reliable method of acute closed chest coronary artery occlusion with a simple, externally controlled, occluding apparatus was described. Preliminary studies were conducted on the pig rather than the dog because of the greater uniformity of the coronary circulation in the former.[1, 9] To further clarify this subject these studies have been extended to 145 successful acute closed chest coronary artery occlusions over a period of 3½ years. The control group was enlarged. Several antifibrillatory agents and surgical procedures were tested and form the basis for this report.

MATERIALS AND METHODS

Young, apparently healthy, stockyard pigs (12 to 30 Kg.) were anesthetized with intraperitoneal chloral hydrate (300 mg. per kilogram of body weight) supplemented as necessary with intravenous Surital (thiamylal sodium) 50 to 75 mg. Transglottic intubation was performed and ventilation was conducted with an automatic respirator using compressed air. Surgical procedures were conducted in an air-conditioned unit. Left thoracotomy was performed through the fourth or fifth intercostal space and the pericardial sac was opened anterior to the phrenic nerve. The left anterior descending branch was dissected free at the bifurcation of the left coronary artery. The coronary artery occluding apparatus† was installed at the origin of the left anterior descending branch. Details of the apparatus have been previously described.[4] Briefly, a plastic snare was passed around the test coronary artery with ample slack to avoid compression of the vessel. The relationship of the

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snare to the axis of the vessel was maintained by a plastic platform which overrides the vessel to be occluded and which was balanced by sutures in the adjacent epicardium. A flexible plastic cable encasing the plastic cord passed from the platform through the thorax and was carried to the exterior between the ribs to the skin where the control side of the apparatus was secured. Two to 4 hours after chest closure, acute, one-stage occlusion of the anterior descending branch was performed by simply pulling the Teflon cable taut and then fixing its position. During the postoperative interval, underwater-seal chest drainage was maintained, and at the time the coronary occlusion was performed the animals were awake or responded readily to external stimuli. Electrocardiographic monitoring was done pre- and postoperatively and during the period of acute coronary occlusion.

Seven groups of pigs were studied and were dealt with as follows before testing by acute closed chest coronary artery occlusion.

Group I.—Forty-five control pigs were not pretreated.

Group II.—Eighteen pigs were intravenously given Ro 2-5803* (2, 6-bis (1-piperidyl-methyl)-4 (a, a-dimethylbenzyl) phenol dihydromide) 0.57 to 8.8 mg. per kilogram of body weight and 15 additional pigs were given 20 mg. per kilogram 10 minutes before testing.

Group III.—Fifteen pigs were intravenously given quinidine (5 mg. per kilogram) 10 minutes before testing and an additional 15 pigs were given 20 mg. per kilogram 10 minutes before testing.

Group IV.—Fifteen pigs, 3 groups of 5, were intravenously given Pronestyl (procaine amide hydrochloride) 15, 25, and 50 mg. per kilogram of body weight, respectively, 10 minutes before testing.

Group V.—Ten pigs were subjected to acute extrapleural ligation of the internal mammary arteries in the second or third intercostal spaces followed immediately by thoracotomy and installation of the occluding apparatus. Closed chest coronary artery occlusion was conducted as described 2 to 4 hours postoperatively.

Group VI.—Nine pigs were subjected to acute extrapleural ligation of the internal mammary arteries at the second or third intercostal spaces and tested by closed chest coronary artery occlusion 58 to 69 days later. The tenth animal in this group died of pneumonia 30 days after internal mammary artery ligation.

Group VII.—Eighteen pigs were subjected to the Beck I operation including abrasion of the epicardium and pericardium, partial ligation of the coronary sinus over a 3 mm. probe, and instillation of 1 Gm. of finely ground asbestos into the pericardial sac. Seventeen of 18 pigs had a large azygos vein in the left thorax emptying into the coronary sinus. This was ligated just proximal to the point of entry. These animals were challenged by closed chest coronary artery occlusion 52 to 102 days later. Five additional animals in this group died in the postoperative period before being tested. Pneumonia and empyema were the causes of death.

*Hoffmann-La Roche, Nutley, N. J.

With due consideration to the possibility of a seasonal factor influencing the results, the periods during which the 145 tests were performed are given in Table I.

TABLE I

Group I—Controls
15 Experiments Jan.-June, 1956
15 Experiments Jan.-June, 1957
15 Experiments April-June, 1958
Group II—Ro. 2-5803 Jan.-June, 1956
Group III—Quinidine Jan.-June, 1957
Group IV—Pronestyl July, Aug., Sept., 1957
Group V—Acute internal mammary ligation Jan.-April, 1958
Group VI—Chronic internal mammary ligation Jan.-March, 1958
Group VII—Beck I operation Nov., 1957—March, 1958

RESULTS

In the control group of 45 pigs there was 100 per cent mortality. Two-thirds died of ventricular fibrillation within 1½ to 5 minutes. The longest survival time in this group was 27½ minutes. Others[7] have reported similar results in open chest experiments.

Accordingly, in this report survival beyond 30 minutes but less than 24 hours has been classified as an acute survival. Survival beyond 24 hours has been classified as a chronic survival.

The results are shown graphically in Figs. 1-8 and are summarized in Fig. 9. Since the preparation of these graphs, 15 additional control studies have been performed making the control group 45 rather than 30 (Fig. 1) and the total experiments 145 rather than 130 (Fig. 9). In all instances marked electrocardiographic changes followed acute coronary occlusion. Some aspects of the electrocardiographic studies have been reported[8] and additional details will form the basis of a separate report.

Animals surviving the challenge later died or were sacrificed upon the days indicated in the graphs. The site and completeness of the coronary occlusion were invariably confirmed in each instance. All survivals classified as chronic survivors showed typical infarcts in the area of myocardium served by the occluded anterior descending branch (Fig. 10). Histologic studies confirmed the gross pathology.

DISCUSSION

The selection of the pig rather than the dog for the testing of antifibrillatory agents and surgical procedures designed to protect against coronary artery ligation has the distinct advantage of uniformity and duplicability in the control studies. The decisiveness of ventricular fibrillation in 100 per cent of 45 control animals leaves little margin for doubt regarding the consequences of acute coronary occlusion in the pig. The antithesis is true for the dog. The technique of closed chest coronary occlusion described has been found simple and uniformly accurate. To minimize, control, or remove such variables as the open chest, changes in pH secondary to respiration, and the effects of anesthesia is highly desirable in the study of ventricular fibrillation.

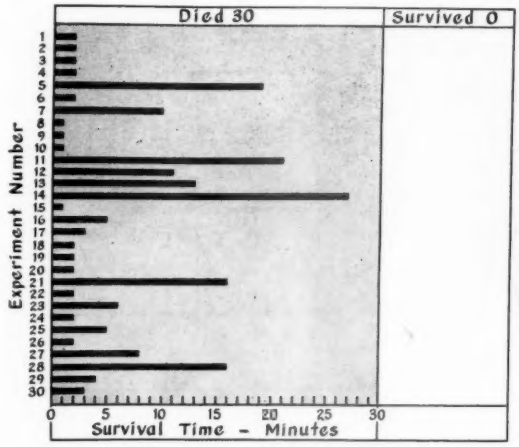


Fig. 1.

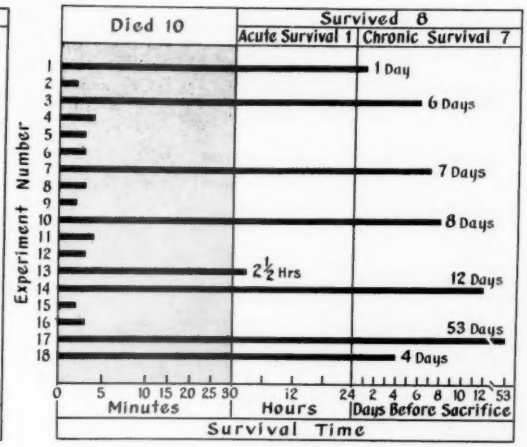


Fig. 2.

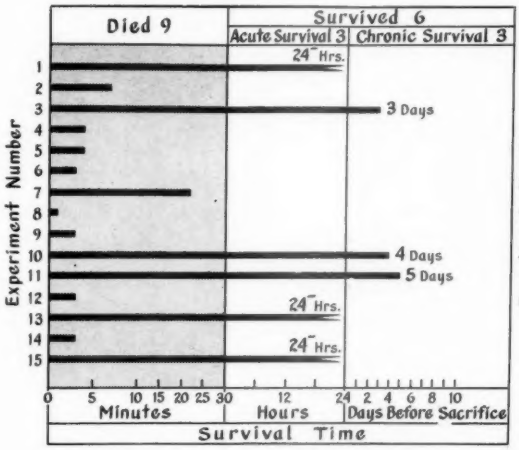
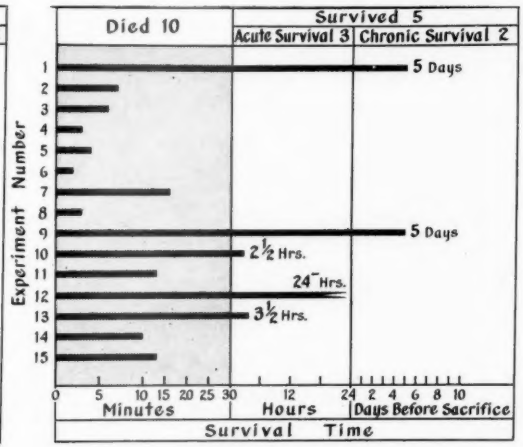


Fig. 3.



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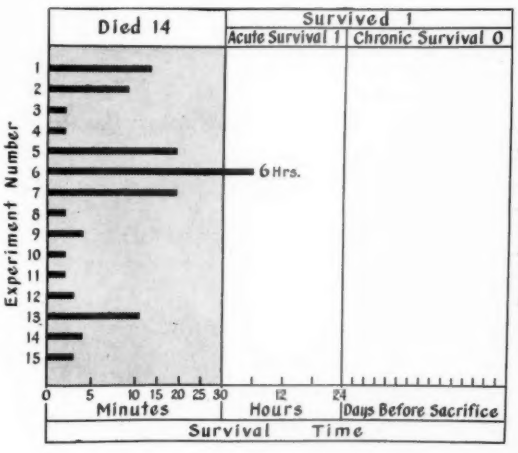

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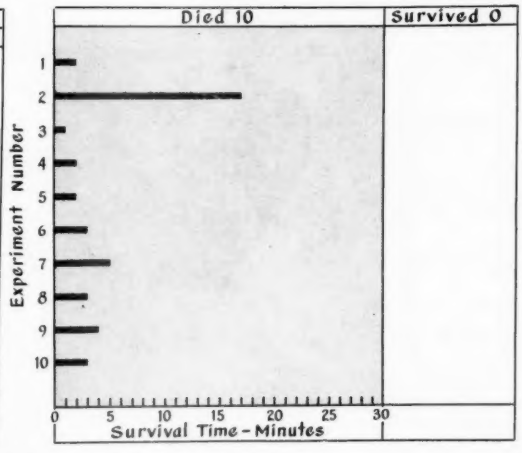

Fig. 6.

Fig. 1.—Control group of 30 pigs. Survival 0 per cent.

Fig. 2.—Ro 2-5803 pretreatment group of 18 pigs. Survival 44.4 per cent.

Fig. 3.—Quinidine pretreatment group of 15 pigs (5 mg. per kilogram). Survival 40 per cent.

Fig. 4.—Quinidine pretreatment group of 15 pigs (20 mg. per kilogram). Survival 33.3 per cent.

Fig. 5.—Pronestyl pretreatment group of 15 pigs (15 to 50 mg. per kilogram). Survival 6.6 per cent.

Fig. 6.—Acute internal mammary artery ligation group of 10 pigs. Survival 0 per cent.

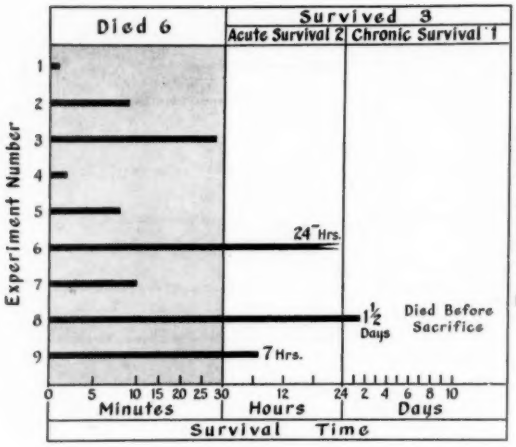

Fig. 7.

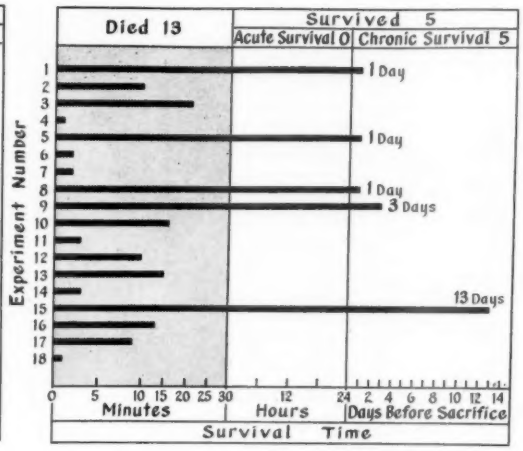

Fig. 8.

Fig. 7.—Chronic internal mammary artery ligation group of 9 pigs. Survival 33.3 per cent.

Fig. 8.—Beck I procedure group of 18 pigs. Survival 27.7 per cent.

Treatment	No. of Animals	Survived	Survival % 20 40 60
Control	30	0	0
Ro 2-5803	18	8	44.4
Quinidine 5 mgms/kg	15	5	33.3
Quinidine 20 mgms/kg	15	6	40
Pronestyl	15	1	6.6
Acute Int. Mammary Lig.	10	0	0
Chronic Int. Mammary Lig.	9	3	33.3
Beck I Operation	18	5	27.7

Acute Survival ⟵ Chronic Survival

Fig. 9.—Summary of 130 experiments.

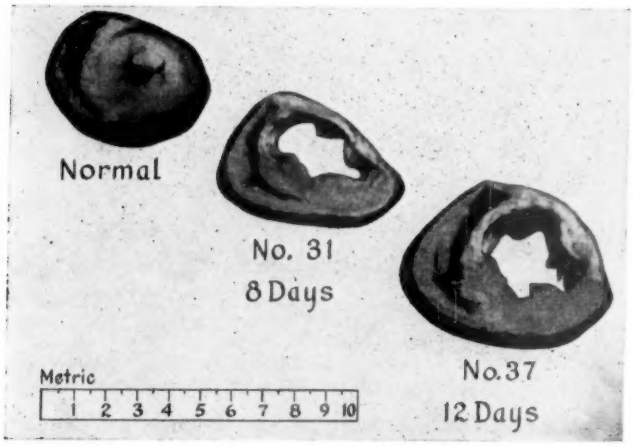

Fig. 10.—Pig heart infarcts following coronary artery occlusion.

The modus operandi for protection against ventricular fibrillation is not lucid. Although previous studies by us[6] regarding the directional flow of an extracoronary blood source would support the augmentation of coronary blood supply by a surgical procedure, more recent studies[2, 5] concerning the movement of Evans Blue dye in the pig myocardium following coronary ligation would indicate that the protective mechanism against ventricular fibrillation need not be based upon improving the blood supply to the ischemic area served by a ligated vessel. The common property of nearly all surgical "revascularizing" procedures is the alteration of the epicardium and pericardium. This aspect of the problem is receiving further attention.

SUMMARY AND CONCLUSIONS

1. A total of 145 pigs were challenged by a simple method of closed chest coronary occlusion, left anterior descending branch.

2. In the control group of 45 pigs, 100 per cent mortality resulted due to ventricular fibrillation which occurred 1½ to 5 minutes following the occlusion in two-thirds of the animals. The longest survival time in this group was 27½ minutes.

3. Pretreatment by antifibrillatory agents and surgical procedures gave the following total, acute, and chronic survival percentages: Ro 2-5803 44.4 per cent (acute 5.5, chronic 38.9); quinidine 36.6 per cent (acute 20, chronic 16.6); Pronestyl 6.6 per cent (acute 6.6); acute internal mammary artery ligation 0 per cent; chronic internal mammary artery ligation 33.3 per cent (acute 22.2, chronic 11.1); and Beck I operation 27.7 per cent (chronic 27.7).

4. The incidence of ventricular fibrillation in the pig due to acute closed chest coronary occlusion, left anterior descending branch at the bifurcation, can be reduced by several antifibrillatory agents and surgical procedures.

5. The data are statistically significant at the 1 per cent level.

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PROGRESS IN SYNTHETIC GRAFT DEVELOPMENT—AN IMPROVED CRIMPED GRAFT OF TEFLON

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WITH the passage of time it is becoming increasingly clear that arterial homografts are less than ideal vascular substitutes because of degenerative changes that weaken the wall with occasional rupture or obstruct the lumen with resulting thrombosis. A durable, readily available artificial graft is therefore being sought in many quarters. Before an ideal substitute can be developed it is necessary to define the desirable characteristics of such a graft. There is not yet uniform agreement as to the properties of the best possible vascular prosthesis. It is the purpose of this paper to discuss those characteristics which seem desirable in artificial arteries and to describe our efforts to approach this "ideal."

CHOICE OF MATERIAL OR FIBER

Solid tubes of many materials (paraffin-lined glass, gold, polyethylene, and Lucite) have been tried. Some of these substances such as methyl methacrylate[13] will function in larger vessels such as the thoracic aorta of dogs, but no solid tube functions satisfactorily in small vessels.[2]

Considerable interest was expressed several years ago in Ivalon sponge as an arterial graft.[15, 16] This solid form of polyvinyl alcohol can be shaped into flexible tubes which are very easy to suture. Unfortunately the tensile strength of this material is low and the incidence of disruption and thrombosis is high.[10] It has, therefore, been abandoned as a prosthesis by most surgeons.

Human and animal tissues have been treated in various ways to make more acceptable substitutes than homografts. Human skin, dermis, intestine, and animal vessels, denatured to reduce the immune response, have been or are being tested. To date these substances have not been impressive either as safe or durable grafts.

Since the introduction by Voorhees, Jaretzki, and Blakemore[17] of the possibilities of synthetic fabrics as substitutes for arteries, the principal attack on the problem has been along these lines. Numerous articles comparing various

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The technical development of crimped Teflon tubes was made possible by Norman C. Jeckel, U. S. Catheter & Instrument Corporation, Glenn Falls, N. Y. These tubes are distributed by C. R. Bard, Inc., Summit, N. J.

fibers, weaves, knits, and so forth, have appeared. Long-term studies of fabric tubes implanted in animals are now being reported from several sources with quite uniform conclusions in regard to characteristics of the principal fibers presently being used. Vinyon "N" has the disadvantage of a low melting point which prevents sterilization by autoclaving and has been eliminated from the "ideal" class because of this. Orlon can be autoclaved but is less desirable than Dacron or Teflon because it incites greater tissue reaction. Nylon was one of the early favorites because of its great tensible strength. It was chosen in our laboratory because of its strength but also because it could most readily be chemically modified (that is, crimped with dilute formic acid). Although nylon has proved most durable to repeated mechanical stress such as is needed in automobile and airplane tire cord, long-term animal tests prove that it loses tensile strength rapidly when bathed by tissue fluids. Harrison[11] found as much as 90 per cent strength loss in 2 years time. His studies were conducted with tubes made of 70 denier nylon cloth, a very fine fiber with large surface area per unit of weight. The crimped nylon tubes studied in this laboratory[4] showed only 30 per cent loss in 2 years on the average, but these grafts were made with large fibers of 210 denier nylon. This seems to indicate that loss of tensile strength is related to the surface area exposed to tissue acids, since large diameter fibers present relatively smaller surfaces. After 2 years there is little further tensile strength loss in the crimped nylon tubes. Thousands of these tubes have been used in humans in the past 3 years and there have been no cases of graft dilatation or disruption. Nylon has an initial tensile strength that is so great that loss of 30 per cent is insignificant. Nevertheless, we agree that ideally a synthetic graft should maintain its original tensile strength after implantation. Teflon is superior to all other fibers in this regard (Table I), showing no loss of strength after 2 years.

TABLE I. TENSILE STRENGTH LOSS OF SYNTHETIC GRAFTS AFTER 100 DAYS IMPLANTATION

Nylon (calendered)	−81.0%
Orlon	− 6.9%
Dacron	−10.1%
Teflon	+ 3.2%

Figures quoted are averages based on Harrison's results[12] in animals sacrificed more than 100 days after implantation. (From Harrison, J. H.: Am. J. Surg. 95: 16, 1958.)

Another most important characteristic of the arterial graft fiber is the amount of tissue reaction it stimulates. The more reaction a fiber produces, the more it acts as a foreign body, causing an inflammatory deposition of fibrin in and around the graft. The degree of this reaction determines the thickness of the fibrin lining the inside of the graft after implantation. This is often a critical factor in small grafts as this lining may narrow or occlude the lumen enough to cause thrombosis. Nylon tubes form a lining which averages 2 mm. in thickness, while Teflon tubes, at the other end of the scale, develop a lining 0.5 to 1.0 mm. in thickness. Dacron and Orlon tubes form a lining 1.0 to 2.0 mm. thick.

A third important property of synthetic grafts which is related to the degree of biologic reaction of the fiber is the length of time it takes for the neointima to heal and become firmly attached to the inside of the tube. In nylon grafts the fibrous lining can be lifted out for 4 to 6 months before attachment and organization of the lining occurs. Tubes of Dacron and Orlon show slight superiority to nylon with attachment occurring in 3 to 6 months. Teflon tubes produce an attached lining in 2 to 3 weeks and healing of this lining is complete in 4 to 8 weeks. Early attachment of the fibrin lining is important to reduce the chance of partial detachment of a flap with occlusion of the lumen and thrombosis.[3] Early organization and healing of the neointima is desirable because only the healed lining offers an unwettable surface to contact with blood. Temporary stasis of blood in an unhealed graft may result in thrombus formation on granulating surfaces.[5]

It is interesting that, in the three important characteristics of synthetic fibers when used as artery grafts, (1) retention of tensile strength, (2) thickness of the fibrin lining, and (3) speed of healing and attachment of the fibrin lining, the four most popular fibers, nylon, Orlon, Dacron, and Teflon, are related in the same order as their degree of water absorption. Teflon absorbs no water, Dacron 0.1 per cent, and nylon 4 per cent. It is quite likely that the degree of tissue reaction stimulated by each fiber is directly related to the amount of tissue fluid absorbed. (Table II.)

TABLE II. WATER ABSORPTION CHART (IMMERSION AT 25° C.)

Nylon	4%
Orlon	1%
Vinyon "N"	0.1%
Dacron	0.1%
Teflon	0

From "Textile Handbook" by Milton Harris Research Laboratories, 1246 Taylor Street N. W., Washington D. C.

By all criteria thus far evaluated then, Teflon would appear to be the superior fiber for arterial grafts. This is supported by the careful experimental and clinical work of Merendino, Girvin, and Thomas[8, 9, 14] and by the extensive studies of Harrison.[10-12] Teflon has one additional property not yet mentioned; it is superior to all other known fibers in flex abrasion resistance. This is the degree of sawing or cutting of the fiber by the adjacent fiber on repeated flexion. Glass fiber is one of the worst from this standpoint. It can cut another fiber without difficulty. The slippery feel of Teflon yarn, another evidence of its lack of water absorption, is the cause of such low flex abrasion.

Teflon fiber comes in the form of a brown yarn. The brown color is a carbon impurity which has been demonstrated by Harrison[12] and confirmed here to stimulate increased tissue reaction and slow the healing of the graft lining. It is now considered desirable to purify or bleach the yarn to remove this brown color. This can be done by boiling the yarn in nitric acid for several hours. The resistance of Teflon is well demonstrated by the fact that this corrosive acid treatment causes no loss of tensile strength, and no change in the water-repellent

properties of Teflon. The acid which cannot penetrate the Teflon fiber but reacts on surface contaminants only is carefully neutralized by boiling in an alkali. The pH of each batch of grafts is carefully tested to be sure no acid reaction remains. Animal observations using grafts so treated have shown much less tissue reaction than in unbleached Teflon grafts.

FORMATION OF A FABRIC TUBE

The original technique devised by Voorhees, Jaretzki, and Blakemore[17] for making a fabric tube consisted of sewing a folded piece of cloth with a longitudinal seam. Such a seam has several disadvantages. It makes suturing more difficult at the seam; the tube is less flexible and more likely to wrinkle. Cases of fatal seam disruption have been reported. It seems quite certain, therefore, that the ultimate in arterial grafts will be seamless. This is especially true since it is so easy technically to produce seamless tubes by weaving, braiding, or knitting. With present-day textile machinery it is possible to fabricate tubes of various sizes, Y tubes, and tubes with tapered ends for adjustment to dilated arteries.

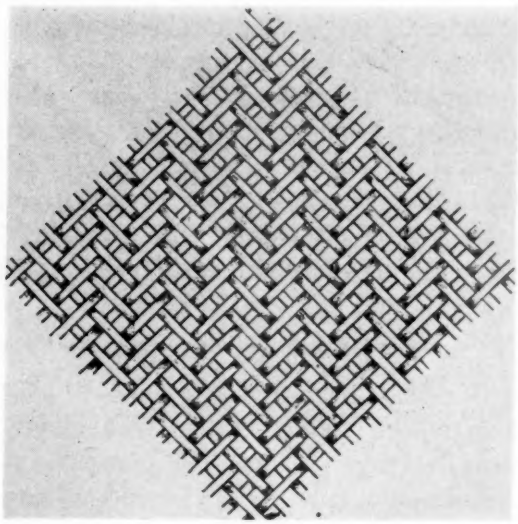
PREPARATION OF A TUBE END THAT CAN BE SUTURED

A tubular piece of cloth can always be turned back at the end to allow a double layer for suturing to the patient's artery. This was the earliest technique described for preventing fraying.[17] This is undoubtedly a satisfactory technique for end-to-end anastomosis of a tubular cloth graft to an artery but it is not adaptable to certain other situations frequently encountered in arterial surgery. The end-to-side anastomosis is currently being used more and more often with the popular technique of bypassing arterial obstructions. To perform such an anastomosis, it is quite advantageous to bevel the end of the graft at an angle of approximately 45 degrees, thus reducing the angulation of the tube necessary adjacent to the anastomosis. This reduced the chance of wrinkling or kinking of the graft. This beveling of the tube makes turning a cuff difficult and it seems much more desirable to have a graft that can be cut and sutured at any desired point or angle without the necessity of cuffing. There is a growing need for a graft with right angle branches, as more complicated aneurysms and obstructions are resected. Since the proper size and origin of the branch often cannot be predicted prior to operation, there is need for a graft to which a branch can be sutured with ease at the operating table. This is the second reason why the "ideal" graft should have as one of its characteristics the capability of holding sutures anywhere a hole may be cut in it for a branch.

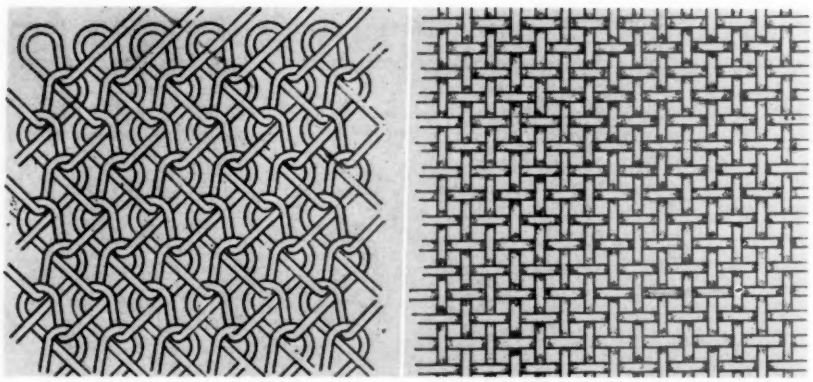
One effective techniue for preparing the end of a tube graft to hold sutures is heat sealing. If the end is held in a flame or touched with actual cautery, the threads of any fabric can be melted and fraying prevented by agglutination of the fibers. The chief disadvantage of using this maneuver to prevent fraying is the explosive hazard if certain anesthetic agents are used.

The type of fabrication of the tube graft will determine the degree fraying of the cut end. There are three basic methods of manufacturing seamless tubes of fabric: braiding, knitting, and weaving. There is a distinct difference in

fabrics made by these three methods which is reflected in the physical properties of the finished tubular product (Fig. 1). In *braiding* a seamless tube there are a fixed number of strands of yarn, usually held in a vertical position, in a circle. These are all constantly in motion intertwining—half of the strands going clockwise in the circle and half counter clockwise. In *knitting* a tube, there are a fixed number of knitting needless held in a circle while a single strand of yarn is fed around the circle to each needle. Each needle produces a stitch so that



A.



B. *C.*

Fig. 1.—*A*, Section of tubular braid. Each thread passes under two and over two. *B*. Section of knit. The thread forms a series of links or stitches. *C*, Section of tubular weave. Each thread has a pattern of under one and over one.

the fabric is composed of a series of interlocking links. A *woven* seamless tube consists of a number of warp threads with a filling thread called the weft or fill which goes under and over each warp so that the finished tubular fabric is the same as the age-old flat woven fabrics we commonly call cloth. The machine for weaving is called a loom.

The ends of a braided tube are least satisfactory from the standpoint of fraying. A woven tube will resist fraying in direct proportion to how tightly

the threads are "packed" together on the loom. It is possible to manufacture a tightly woven tube that can be sutured even without heat sealing, provided a moderate amount of care is observed at surgery in cutting and handling with forceps. This tube has the added advantage of low porosity as will be discussed later.

A knitted tube is superior to woven or braided tubes in resistance to fraying since it is fabricated of interlocking stitches. It is almost impossible to make a knitted tube fray, and a hole can be cut in the side of the tube for a branch without raveling.

POROSITY

A completely nonporous plastic tube has been uniformly unsuccessful in replacing small vessels. The most likely explanation for this is that the fibrin lining cannot heal and form an unwettable smooth surface and cannot become attached.[3] Slight porosity seems essential to allow capillary nourishment of the neointima and to promote its early attachment to the framework. Too great a degree of porosity, on the other hand, leads to serious blood loss at the time of implantation. The happy medium can be approached in several ways.

Porosity of braided nylon tubes can be controlled chemically by the concentration of formic acid used to set the crimps. This acid semisolvent causes the nylon fibers to swell and to adhere to adjacent fibers. Unfortunately, there is no known solvent for Teflon, so some other method than chemical control of porosity is necessary with this fiber. There is a limit to the tightness of a knitted tube because each interlocking stitch is made around a knitting needle and the pores can be made no smaller than the diameter of this small needle. Although the knitted tube ends hold sutures extremely well, a knitted tube is quite porous. The size of the openings can be reduced slightly by impregnating the graft with a dispersion of some inert material which reduces the size of the holes, but this causes slight stiffening of the graft. Careful preclotting of the graft with the patient's own blood before implantation of the tube reduces blood loss in most patients to a minor problem. The technique, described in the previous section, for tight-weaving cylindrical tubes is a superior method to any now known for producing minimum but adequate porosity. Tubes in this tightly woven form can be implanted without preclotting without fear of blood loss.

PREVENTION OF KINKING

Experimental work with animals using collapsible cloth tube grafts soon demonstrated the likelihood of wrinkling or kinking if the graft were not sutured with exactly the correct amount of tension. This led to what has been called "wrinkle thrombosis."[18] With the development of the bypass technique around occluded segments of artery and with more extensive artery replacement, especially across flexible joints such as the groin, axilla, neck, and knee, it became evident that some mechanism to minimize wrinkling or kinking would be an essential in synthetic grafts. Two methods have evolved to avoid kinking: (1) the use of elastic or stretch yarn and (2) the incorporation of corrugations or crimps in the tube. Although stretch yarn is undoubtedly more flexible than

ordinary yarn, tubes of this elastic material still have one disadvantage—they are completely and flaccidly collapsible. Even an empty arterial homograft maintains its cylindrical shape better than a collapsible cloth tube, and we feel that this is an important characteristic of arteries for maintaing a patent lumen despite acute angulation. Corrugating the synthetic tube makes it possible to flex acutely without kinking partly because this tube is relatively noncollapsible. The major criticism leveled at this technique of using corrugated tubes has been the possibility that the irregular inside lining might produce turbulence or increased resistance to blood flow and promote thrombosis. Extensive animal experiments and many clinical cases now document that this is not so.[6] Our early animal work with small caliber nylon grafts of 6 mm. inside diameter resulted in only 5 per cent thrombosis.[7] It was learned soon that the slight internal irregularities from the crimps were smoothed out by fibrin deposition in the concavities in a matter of minutes. It seems well established now that shallow corrugations do not lead to greater risk of thrombosis, even in small grafts, and are quite satisfactory in preventing kinking across areas of flexion.

An unexpected advantage of crimping has recently become apparent. In suturing side branches to a larger aortic graft it is difficult even at the operating table to estimate exactly where the hole should be made in the side of the aortic segment. If this opening is not made at exactly the right spot, angulation of the branch will occur. This angulation is not dangerous if a relatively noncollapsible flexible crimped tube is used but kinking and thrombosis is difficult to avoid with a collapsible cloth branch.

DISCUSSION

From the above considerations of desirable characteristics, our efforts have been directed for the past 2 years toward development of crimped tubular grafts of Teflon. Since there is no chemical method of setting corrugations in Teflon tubes, a high temperature bake is used instead. This heat sets the crimps quite satisfactorily. Seamless crimped Teflon tubes of two basically different constructions have been extensively studied both in animal and man: (1) a knitted tube impregnated with a dispersion of tetrafluorethylene resin to reduce porosity and (2) a tightly "packed" woven tube of low porosity. The tubes of knitted construction hold sutures superbly, but careful preclotting with the patient's blood is necessary to prevent excessive blood loss after restoration of blood flow. Branches can be sutured to the side of such tubes without difficulty (Fig. 2). Tubes of the tight weave type, on the other hand, simply "sweat" a few red cells and serum after the clamps are released and need no preliminary clotting. As mentioned before, these low porosity tubes are considered safer in hypertensive patients, in those with possible clotting defects, and in those in whom heparin is used. A recent case in our clinic* demonstrated the advantages of this woven construction. The patient presented with an extensive luetic fusiform aneurysm of the descending aorta. Using the technique of

*Operated upon by Dr. Champ Lyons.

temporary pump bypass described by Cooley, DeBakey, and Morris,[1] shunting blood from the left auricle to the femoral artery, the entire descending aorta from left subclavian to diaphragm was removed. A ¾-inch I.D. woven tube was sutured into the resulting defect. This tube was not preclotted, and despite full heparinization of the patient there was no blood loss through the graft wall.

The tubes of woven construction do not hold sutures quite as well as knitted tubes but fraying can be avoided by placement of the sutures at least 1 mm. back from the cut edge and by careful handling. All difficulty with fraying can be prevented by heat sealing the tube end, but with a little experience this is not necessary. No particular difficulty has been encountered in cutting a hole in the side of a woven tube and suturing in place a right-angled branch.

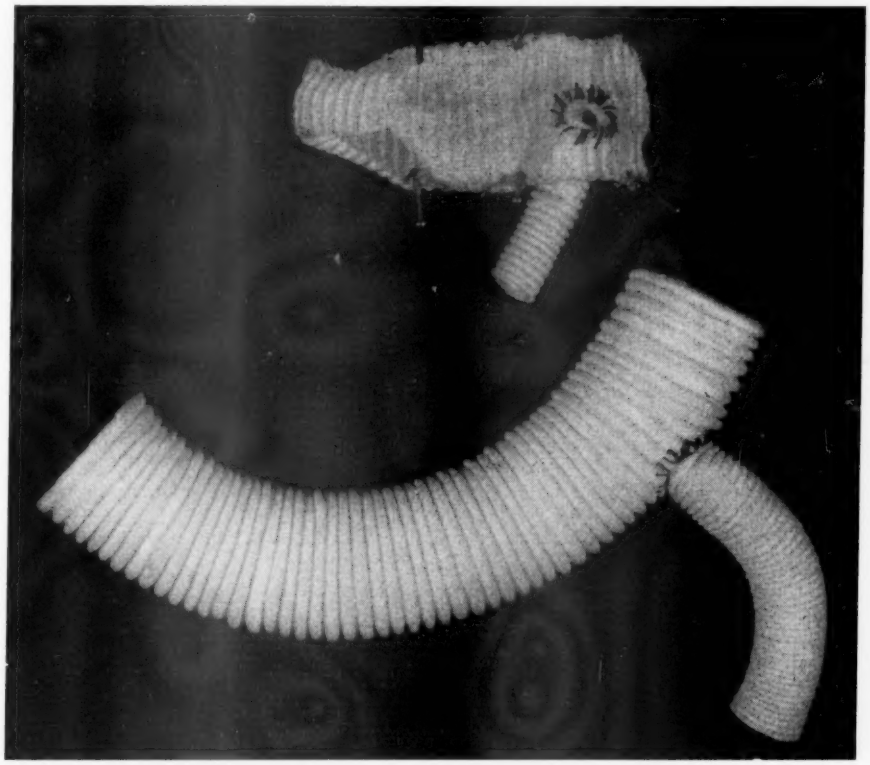


Fig. 2.—Technique of suturing right angle branches is demonstrated. The larger tubes are knitted Teflon, the smaller ones woven.

Dogs sacrificed at regular intervals after insertion of knitted and woven Teflon grafts reveal that the fibrin lining is very thin and transparent, never more than 1 mm. in thickness. This lining becomes firmly attached in one or two weeks—this is months sooner than attachment is secure in nylon, Orlon, or Dacron tubes. The neointima is completely healed in 4 to 8 weeks (Fig. 3). There is no discernible difference in healing or attachment time of the fibrin lining between the porous knitted and the much less porous woven tubes.

Bifurcation grafts can be fabricated of either knitted or woven construction. Clinical experience indicates that two sizes are needed to meet almost all

anatomic situations. One size, principally for replacement of abdominal aortic aneurysms, should have an aortic segment of ¾ inch internal diameter with ⅜-inch I.D. legs. It seems helpful to crimp the aortic section as well as the legs and to taper the upper end to one inch I.D. to make this end adaptable to a dilated aorta (Fig. 4). The tapered portion can be cut off if the aorta is not excessively dilated above the aneurysm. The aortic section of the graft is manufactured quite short to reduce the temptation on the part of the surgeon to leave an aortic segment so long that the legs would be angulated too acutely in joining the iliac arteries. If a replacement for renal, iliac, or superior mesenteric branches is indicated, an additional length of ¾-inch I.D. tubing can be sutured to the aortic end of the bifurcation tube and holes cut at the appropriate location for branches. A smaller sized bifurcation tube is quite helpful in cases of aortic or iliac obstruction. This Y tube has a crimped aortic segment ½ inch I.D. with iliac limbs 5/16 inch I.D. Crimping the aortic segment simplifies the technique of suturing the graft to the side of the aorta in performing a complete aortoiliac bypass without dividing the aorta, a procedure often done in cases of aortic or iliac stenosis without complete occlusion.

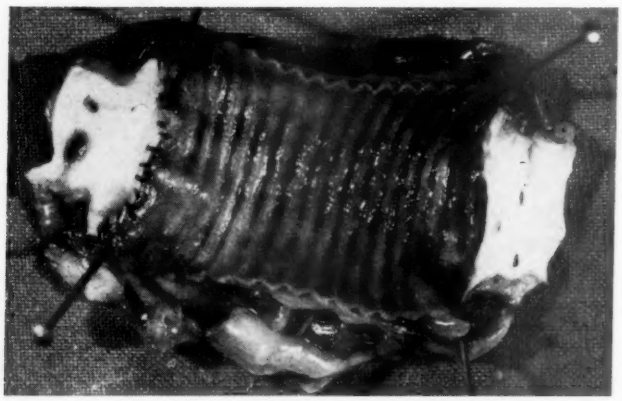
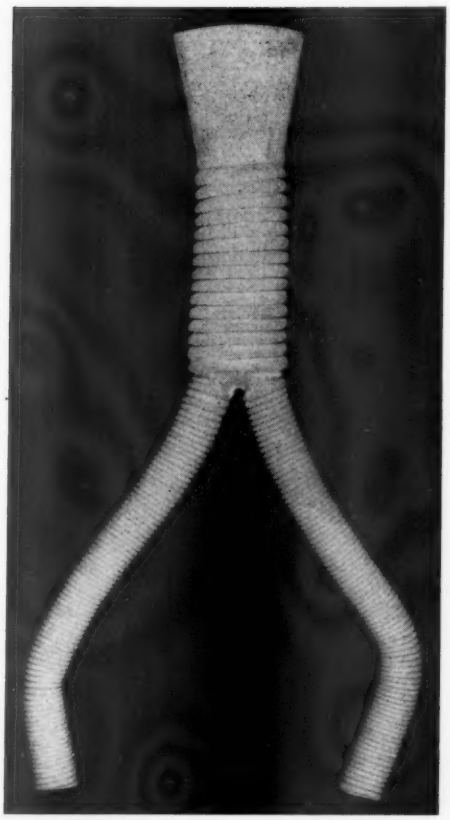


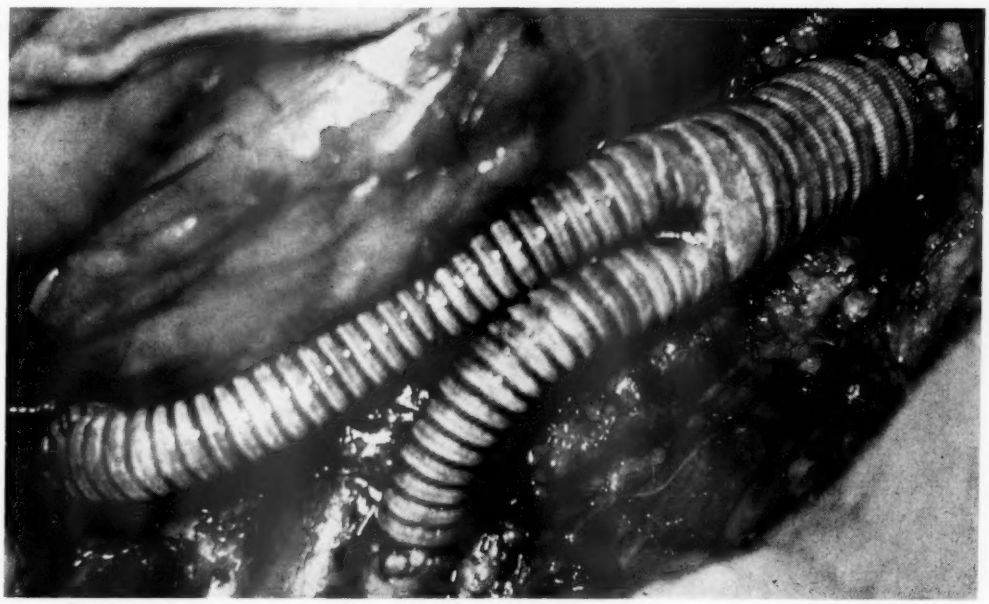
Fig. 3.—The lining of this woven crimped Teflon graft removed 2 weeks after implantation had almost completely healed and was inseparable from the fabric.

Because of the frequent occurrence of dilated aorta proximal or distal to a fusiform thoracic aneurysm, tubes as large as 1¼ inches I.D. are needed. It is felt that woven tubes with low porosity are definitely safer in the thoracic aorta where aortic pressure is high and the surface area of graft often is large. Here vital organs such as the spinal cord and kidneys tolerate temporary ischemia poorly, and reclamping the knitted grafts to control blood loss through the pores can be a dangerous maneuver. Fraying is no problem in the large woven tube since rather large bites are customarily taken in both the aorta and graft to complete the anastomosis expeditiously.

To date 24 knitted and woven tube grafts have been inserted in peripheral small arteries including femoral, popliteal, brachial, and carotid replacements or bypass grafts. The technical aspects of peripheral artery grafting with Teflon tubes has recently been described.[6] Ten knitted and four woven bifurcation tubes have been employed. Two thoracic-abdominal and four descending



A.



B.

Fig. 4.—*A*, Knitted crimped aortic bifurcation graft of Teflon. *B*, Crimped knitted bifurcation graft replacing an abdominal aortic aneurysm.

thoracic aortic aneurysms have been treated with crimped Teflon. The longest follow-ups are 9 months at present, but there have been no serious graft complications to date.

In this clinic at present the graft of choice is tightly woven crimped Teflon. This tube is soft, pliable, holds a crimp well, and is easily penetrated by the finest needle. With moderate care in cutting and handling, fraying of the ends is no problem even without heat sealing. The low porosity has completely eliminated bleeding problems, without interference with the healing and attachment of the fibrin lining.

SUMMARY

In attempting to develop a safe, simple, durable, and versatile synthetic arterial graft, the superior fiber must first be determined. The most desirable method of producing a tube graft of this fiber must then be explored.

Animal and clinical experience in the last 4 years has led to the following opinions:

Teflon is the most durable of all known fibers, it causes less tissue reaction, and the fibrin neointima heals and becomes attached to the inside far more rapidly than in any other synthetic tube.

Seamless tubes are preferable to those with seams since the former are more flexible, easier to handle, and safer in avoiding wrinkling.

Some method other than cuffing the end of the graft is desirable to prevent fraying. Heat sealing of the end is an effective technique. Knitted tubular grafts are quite resistant to fraying but are moderately porous and careful preclotting is required. Tightly woven tubes can be sutured without fraying if the cut ends are handled with moderate care.

The woven crimped Teflon tubes have the distinct advantage of low porosity which eliminates all problems with oozing through the graft even in hypertensive or heparinized patients. This is the graft of choice in our clinic.

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THE INHIBITION OF THE COAGULASE OF THE STAPHYLOCOCCUS AUREUS BY CONGO RED

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CONGO red has the ability to inhibit the conversion of fibrinogen to fibrin.[2] The clotting of human plasma by staphylococcus coagulase parallels the mechanism of the clotting of fibrinogen by thrombin. Smith and Hale[4] reported that the coagulase was inert as far as the conversion of fibrinogen was concerned. The coagulase was the precursor of a thrombinlike substance which converted fibrinogen into fibrin. The process was analogous to the formation of thrombin from prothrombin by the agency of thrombokinase with the important difference that calcium was not required. If Congo red could inhibit the action of the coagulase of staphylococcus upon human blood plasma, the fact might have clinical significance. A mixture of a broth culture of the *Staphylococcus aureus,* Congo red, and human plasma provided an easy way to test the fundamental concept.

TABLE I. THE RESULTS WITH A 0.1 PER CENT SOLUTION OF CONGO RED

NUMBER OF TEST TUBE	HUMAN PLASMA (C.C.)	CONGO RED (C.C.)	CONGO RED (MG.)	CONCENTRATION OF CONGO RED (PER CENT)	DISTILLED WATER (C.C.)	CULTURE OF STAPHYLOCOCCUS AUREUS (C.C.)	RESULT	TIME (HOURS)
1	0.5	0.0	0.0	0.000	1.2	0.3	+	2
2	0.5	0.1	0.1	0.005	1.1	0.3	+	2
3	0.5	0.2	0.2	0.010	1.0	0.3	+	2
4	0.5	0.3	0.3	0.015	0.9	0.3	+	2
5	0.5	0.4	0.4	0.020	0.8	0.3	+	2
6	0.5	0.5	0.5	0.025	0.7	0.3	+	2
7	0.5	0.6	0.6	0.030	0.6	0.3	+	2
8	0.5	0.7	0.7	0.035	0.5	0.3	+	2
9	0.5	0.8	0.8	0.040	0.4	0.3	±	6
10	0.5	0.9	0.9	0.045	0.3	0.3	±	6
11	0.5	1.0	1.0	0.050	0.2	0.3	±	6
12	0.5	1.1	1.1	0.055	0.1	0.3	±	6
13	0.5	1.2	1.2	0.060	0.0	0.3	±	6
14	0.5	1.2	1.2	0.060	0.3	0.0	–	6

+ = Solid clot present.
± = Loose clot present.
– = Clot not present.

Fresh broth cultures of *Staphylococcus aureus* about 20 hours old provided the source of the coagulase. This was mixed with Congo red and human plasma. The results of using a 0.1 per cent solution of Congo red (Table I), a 0.2 per cent

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solution (Table II), and a 0.3 per cent solution (Table III) demonstrated a critical level of Congo red which inhibited the action of the coagulase of the *Staphylococcus aureus* upon human plasma to prevent clotting of the human plasma.

TABLE II. THE RESULTS WITH A 0.2 PER CENT SOLUTION OF CONGO RED

NUMBER OF TEST TUBE	HUMAN PLASMA (C.C.)	CONGO RED (C.C.)	CONGO RED (MG.)	CONCENTRATION OF CONGO RED (PER CENT)	DISTILLED WATER (C.C.)	CULTURE OF STAPHYLOCOCCUS AUREUS (C.C.)	RESULT	TIME (HOURS)
1	0.5	0.0	0.0	0.000	1.2	0.3	+	2
2	0.5	0.1	0.2	0.010	1.1	0.3	+	2
3	0.5	0.2	0.4	0.020	1.0	0.3	+	2
4	0.5	0.3	0.6	0.030	0.9	0.3	±	6
5	0.5	0.4	0.8	0.040	0.8	0.3	±	6
6	0.5	0.5	1.0	0.050	0.7	0.3	±	6
7	0.5	0.6	1.2	0.060	0.6	0.3	±	6
8	0.5	0.7	1.4	0.070	0.5	0.3	±	6
9	0.5	0.8	1.6	0.080	0.4	0.3	±	6
10	0.5	0.9	1.8	0.090	0.3	0.3	±	6
11	0.5	1.0	2.0	0.100	0.2	0.3	±	6
12	0.5	1.1	2.2	0.110	0.1	0.3	±	6
13	0.5	1.2	2.4	0.120	0.0	0.3	±	6
14	0.5	1.2	2.4	0.120	0.3	0.0	–	6

+ = Solid clot present.
± = Loose clot present.
– = Clot not present.

TABLE III. THE RESULTS WITH A 0.3 PER CENT SOLUTION OF CONGO RED

NUMBER OF TEST TUBE	HUMAN PLASMA (C.C.)	CONGO RED (C.C.)	CONGO RED (MG.)	CONCENTRATION OF CONGO RED (PER CENT)	DISTILLED WATER (C.C.)	CULTURE OF STAPHYLOCOCCUS AUREUS (C.C.)	RESULT	TIME (HOURS)
1	0.5	0.0	0.0	0.000	1.2	0.3	+	2
2	0.5	0.1	0.3	0.015	1.1	0.3	+	2
3	0.5	0.2	0.6	0.030	1.0	0.3	+	2
4	0.5	0.3	0.9	0.045	0.9	0.3	–	6
5	0.5	0.4	1.2	0.060	0.8	0.3	–	6
6	0.5	0.5	1.5	0.075	0.7	0.3	–	6
7	0.5	0.6	1.8	0.090	0.6	0.3	–	6
8	0.5	0.7	2.1	0.105	0.5	0.3	–	6
9	0.5	0.8	2.4	0.120	0.4	0.3	–	6
10	0.5	0.9	2.7	0.135	0.3	0.3	–	6
11	0.5	1.0	3.0	0.150	0.2	0.3	–	6
12	0.5	1.1	3.3	0.165	0.1	0.3	–	6
13	0.5	1.2	3.6	0.180	0.0	0.3	–	6
14	0.5	1.2	3.6	0.180	0.3	0.0	–	6

+ = Solid clot present.
– = Clot not present.

COMMENT

The production of coagulase by the staphylococcus is related to its pathogenicity.[5] The deposition of fibrinogen about the staphylococci by its enzyme has been reported to inhibit phagocytosis of the staphylococci by human leukocytes.[1] When human leukocytes were allowed to ingest coagulase positive staphylococci in plasma, conspicuously fewer staphylococci were ingested per 100 leukocytes in whole plasma than in defibrinated plasma.[3] In contrast, the phagocytosis of nonpathogenic strains which did not produce coagulase was approximately the same

in both systems and occasionally even less in the defirinated system. The inhibition of the mechanism by Congo red may make the staphylococcus more susceptible to phagocytosis by human leukocytes.

SUMMARY

Congo red had the ability to inhibit the clotting of human plasma by the coagulase of the *Staphylococcus aureus*. This action may make the staphylococcus more susceptible to phagocytosis by human leukocytes.

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TOTAL BILATERAL POLYVINYL URETERAL SUBSTITUTES IN THE DOG

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THE search for a working ureteral substitute has intrigued surgeons for many years. Two channels have been explored by many investigators: (1) ***biologic*** structures, viable and nonviable (veins,[17] arteries,[20] fascia,[14] abdominal wall,[22] Fallopian tubes,[18] rolled bladder wall, [1, 4, 7, 10, 12, 16, 21] skin tubes,[3] and ileum[2]) and (2) *inert nonbiologic* prostheses (Vitallium,[13, 14] tantalum,[15] and polyethylene[5, 8, 9, 19]). Reliable success has been attained only with viable ileal conduits.[23] Other biologic substitutes have sloughed. Hopeful analogies between ureteral substitutes and blood vessel substitutes lead only to failure. Urine is not blood; the biologic product which conducts urine must contain an arterial supply.

Experiments with inert materials have been plagued with two faults: (1) migration of the tubular prosthesis and (2) encrustation of the tube by urinary salts.

Experiments have been performed on 10 dogs at the Veterans Administration Hospital, New York City, New York, in an effort to solve these technical barriers. In an effort to prevent encrustation, we have prepared the ureteral prosthesis from an extruded tube of polymerized polyvinyl chloride. To attain fixation, and thus avoid migration of the tube, we have devised a doubly-flanged prosthesis. The technique and results of these experiments are reported here.

MATERIALS AND METHODS

The ureteral prosthesis (Fig. 1) is prepared from a segment of commercial polyvinyl chloride nasogastric suction tube. Polyvinyl is a resin, a polymer of the—CH_2-CH—radical. The material is faintly bluish in color, tasteless, transparent, and radiolucent. The tubing is soft, flexible, and does not crimp. The tube may be readily cut and sewn.

The tubing is cut into segments 10 inches in length, and to one end of the segment is affixed a flange of the same material. The flange is simply a strip which is wrapped around the tubing to form a small collar, and is held then in cylindrical shape by a suture of No. 32 stainless steel wire. Additional flanges are prepared but are not attached to the prosthesis. One of these separate flanges is affixed to the bladder end of the ureteral prosthesis in the course of the operative procedure. The prosthetic materials are sterilized by overnight immersion in aqueous Zephiran solution.

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Ten mongrel dogs, 9 males and one female, weighing from 60 to 75 pounds, were the subjects of the experiment. General anesthesia was induced with intravenous Nembutal, 60 mg. for every 5 pounds in weight. Intratracheal intubation was used.

A long midline, or pararectus, incision was made through the abdominal wall. The abdominal contents were either packed away or exteriorized in a saline-soaked sterile towel. The peritoneum lateral to the kidney and ureter was longitudinally incised and elevated, exposing the ureter and the renal pelvis. (The dog's pelvis is small and almost invariably of the "intrarenal" variety.) The distal ureter was clamped, divided, and ligated, with 2-0 chromic catgut, near the bladder. A V-shaped incision was made in the ureteral wall a few centimeters below the renal hilum. Through this opening a flexible surgical probe was passed, eye-end first, into the renal pelvis (Fig. 2). The probe then was forced through the renal parenchyma laterally. The unflanged end of the plastic prosthesis was then drawn over the probe and affixed with a silk suture (Fig. 3). The probe was then withdrawn, dragging the prosthesis behind it. Very careful traction must be used at this stage, or the renal pelvis may be evulsed. Traction was continued until the flanged extremity could be palpated at the ureteropelvic junction. The ureteral stump was encircled below the flange with two ties of No. 32 stainless steel wire (Fig. 4).

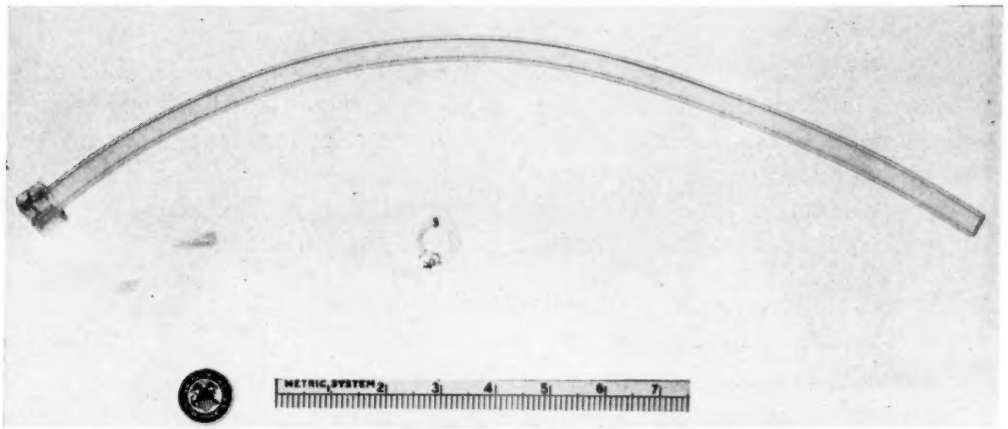


Fig. 1.—The flanged polyvinyl prosthesis. The upper flange is affixed before operation. The bladder flange is affixed after the tube has been drawn into the bladder.

The bladder was opened with a midline incision. A retroperitoneal tunnel to the posterior bladder wall was formed by finger dissection through the lower angle of the posterior peritoneal incision. The probe, still sutured to the distal end of the prosthesis, was passed through this tunnel and forced through the posterior bladder wall, entering the bladder lumen a few millimeters above the trigone (Fig. 5). A second flange was passed over the intravesical portion of the tube. This flange was seated firmly against the bladder wall to take up the slack between kidney and bladder and to prevent postoperative redundancy in the prosthetic length (a cause of hydronephrosis and death in 2 animals). Excess tube, distal to the flange, was excised, and the flange was affixed to the tube

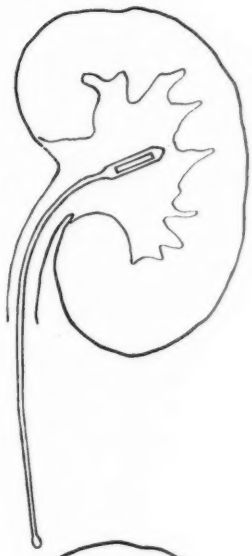


Fig. 2.

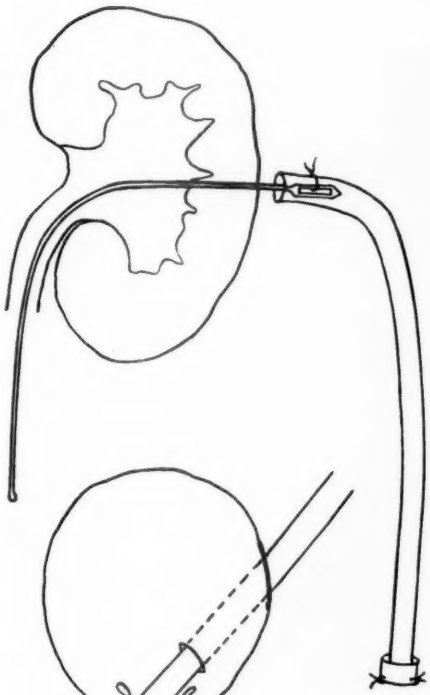
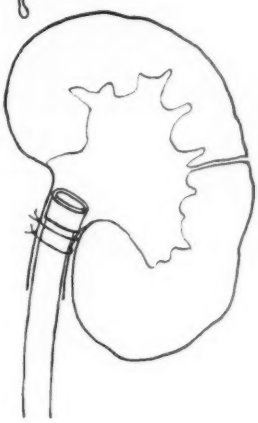


Fig. 3.



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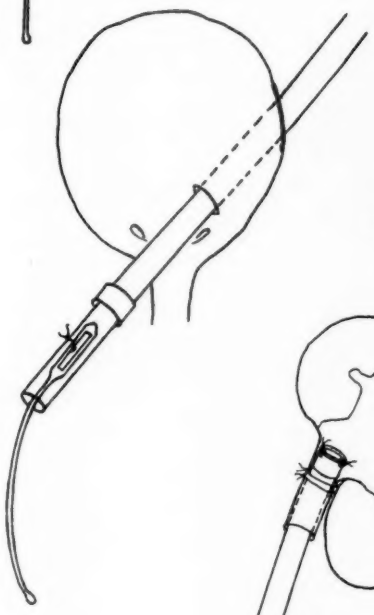

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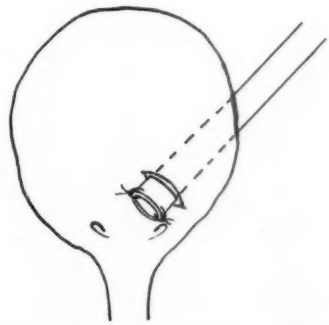

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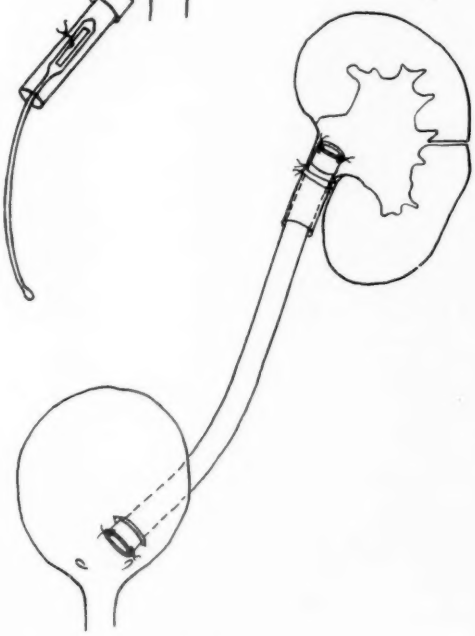

Fig. 7.

Fig. 2.—A flexible probe is inserted into the severed ureter.

Fig. 3.—The probe is forced through the renal parenchyma. The unflanged tip of the prosthesis is passed over the eye of the probe and fixed to the probe with a single silk suture.

Fig. 4.—The tube is drawn into the pelvis until the flanged extremity is arrested by the ureteropelvic junction. This step must be carefully performed to prevent avulsion of the delicate pelvic wall. The ureter is encircled with 2 ties of stainless steel wire just below the flange.

Fig. 5.—The probe is passed through a retroperitoneal tunnel and forced through the posterior bladder wall about 1 cm. above the trigone. The attached tube is drawn into the bladder lumen. The bladder flange is slipped over the tube until it is snug against the epithelial surface.

Fig. 6.—Tubing which protrudes beyond the flange is excised. The flange is fixed to the tube with 2 sutures of No. 32 stainless steel wire. A purse-string suture (not shown) is inserted in the posterior bladder wall.

Fig. 7.—Diagrammatic sketch of the completed procedure.

with two No. 32 stainless steel sutures (Fig. 6). The bladder was closed with a double-layer running suture of 2-0 chromic catgut. The posterior peritoneum was reapproximated with several interrupted sutures of plain catgut to accomplish complete extraperitonealization of the entire prosthesis. Fixation of the kidney (a crucial step in the prevention of prolapse of the prosthesis into the renal pelvis, with subsequent obstruction, hydronephrosis, and death) was accomplished by simple through-and-through suture of the perinephric fat to the ileopsoas muscle. In a few animals the central portion of the prosthesis was encircled with a single tie of No. 32 stainless steel wire which was then sutured to the adjacent ileopsoas muscle. This maneuver was not used in the later and more successful operations. One No. 32 stainless steel purse-string suture was inserted in the posterior bladder wall to surround and fix the prosthesis at the point of entry. No external drainage of any kind was used. The abdominal incision was closed in layers with running sutures of 2-0 chromic catgut. The skin was closed also with running 2-0 chromic catgut.

Intramuscular penicillin (300,000 units) and streptomycin (0.25 Gm.) were administered to every animal twice daily for the first week after operation. Food and water were permitted on the first postoperative day. The dogs were fed Hunt Club dry dog food when they were hungry. Dogs who declined to eat this unpalatable mixture were fed fresh milk, raw beef, and canned Atlantic and Pacific dog food. Liberal amounts of calcium and phosphorus were present in all diets. No supplementary vitamins were administered. Water was permitted ad libitum. Space limitations did not permit runs for the animals. They were kept confined in small cages.

TABLE I. DIMENSIONS OF THE PROSTHESIS

	LENGTH	EXTERNAL DIAMETER	INTERNAL DIAMETER
Tubing	As necessary	4.5 mm.	3.0 mm.
Flange	5 mm.	6.5 mm.	4.5 mm.

These dimensions are those of the tubes used on the last 5 animals. Some variation occurred in the earlier animals.

RESULTS

The period of survival and the cause of death are shown in Table II. Three animals have survived in good health for more than one year. Two of these survivors had bilateral replacement of the ureters. The third survivor had only unilateral replacement. Intravenous pyelograms on the survivors are shown in Figs. 8, 9, 10, and 11.

One animal died of peritonitis on the seventh day. This death could be attributed clearly to urinary leakage. Two animals died of surgical shock, one on the day of operation and one on the first postoperative day. One animal died of respiratory failure in the interval between anesthetic induction and the insertion of the intratracheal tube (this death occurred at the second operation; a unilateral prosthesis was functioning well). One animal died of pneumonia on the ninth day. Two animals died of infected hydronephrosis and uremia, one on the fifty-second day, and the second on the eighty-seventh day.

Fig. 8.

Fig. 9.

Fig. 10.

Fig. 11.

Fig. 8.—An intravenous pyelogram on Dog No. 3. This female animal survived 52 days and died of hydronephrosis and uremia. The effects of migration of the tube are demonstrated. Excess tube projecting into the pelvis caused impingement of the tubular orifice against the pelvic wall, thus producing obstruction and hydronephrosis.

Fig. 9.—An intravenous pyelogram on Dog No. 8. There is excessive tube in the pelvis. In addition, encrustation of the bladder flange occurred, with total obstruction of the prosthesis. The animal made a rapid recovery after the encrusted flange was excised in a secondary operation. This animal is one of the 3 long-term survivors.

Fig. 10.—A 30-minute intravenous pyelogram on Dog No. 6 six months after bilateral total replacement. This animal is in good health 14 months after operation. There is no calcification. The pelves are not dilated. There is normal calyceal cupping. Note that there is no surplusage of prosthesis.

Fig. 11.—A 5-minute intravenous pyelogram on Dog No. 7 three months after total bilateral replacement. There is prompt excretion of dye. There is a suggestion of intrarenal calcification. However, this animal is in good health 14 months after operation. A snug-fitting prosthesis may be observed.

TABLE II.

DOG	SEX	WEIGHT (LBS.)	OPERATION	SURVIVAL	COMMENTS
1	M	70	March 6, 1957	7 days	Dead: peritonitis, urinary leakage
2	M	70	March 19, 1957 April 15, 1957	27 days	Dead: anesthetic fatality, renal inflammation
3	F	60	March 26, 1957	52 days	Dead: unilateral hydronephrosis
4	M	70	April 2, 1957	9 days	Dead: pneumonia
5	M	75	May 20, 1957	1 day	Dead: surgical shock
6	M	70	June 4, 1957		Living and well, normal intravenous pyelogram
7	M	62	June 18, 1957		Living and well, normal intravenous pyelogram
8	M	68	June 28, 1957		Living and well, unilateral vesical flange encrusted
9	M	65	July 29, 1957	87 days	Dead: hydronephrosis
10	M	68	Aug. 5, 1957	0 days	Dead: surgical shock

One animal, on which only unilateral replacement had been performed, refused to eat 2 months after the replacement operation. An intravenous pyelogram showed a nonfunctioning kidney on the operated side and a calcification in the bladder region. The bladder was reopened at a second operation. The prosthesis was found to be completely obstructed by a calcific encrustation which encased the flanged extremity. The tube was transected just above the flange. A gush of purulent urine followed. The bladder was reclosed. This animal made a quick recovery and was in good health 9 months later. He is included among the 3 survivors. This animal represents the sole instance of phosphatic encrustation. Even in the 2 animals which succumbed to obstruction, hydronephrosis, and uremia, there was no encrustation of the prosthesis. Obstruction in each of these animals could be ascribed to redundancy and malposition of the tubes.

Microscopic examination of the kidneys in 2 animals that died from nonrenal causes showed foreign-body giant cell reaction in the renal pelvis and moderate interstitial inflammatory reaction in the renal parenchyma. The grossly purulent urine from one animal that developed hydronephrosis grew out a staphylococcus albus, which was nonhemolytic.

A female dog that survived 2 months and 4 days, dying of unilateral hydronephrosis, was studied for evidence of ureteral regeneration. At autopsy the plastic ureters were snugly encased by overlying peritoneum and underlying muscle. The tissue surface immediately contiguous to the plastic tube was smooth and glistening in appearance, suggesting the reformation of transitional epithelium, a phenomenon which some investigators have alleged will occur.[6, 11] A block of this tissue was excised for microscopic examination. The pathologist (Dr. C. M. Plair) found "a focus of fibrinopurulent exudate with some necrotic material in relation to degenerating muscle fibers and fibroadipose tissue. In some of the fibrous tissue there are small foci of lymphocytes and plasma cells. In one area the striated muscle fibers extend out into the adipose tissue. Diagnosis: Acute and chronic inflammatory reaction involving fibroadipose tissue and skeletal muscle." Evidently, no transitional cells grew along the polyvinyl ureter.

COMMENT

The utilization of doubly-flanged polyvinyl tubes as surgical substitutes for the canine ureter has been shown to be a feasible technique. Survival of three animals for more than one year is evidence that renal excretory requirements, in the dog at least, do not demand a motile conduit between renal pelvis and bladder. Although urinary reflux must, of necessity, be present in these animals, intravenous pyelograms show no resulting renal damage. British surgeons,[9] who used small caliber polyethylene tubes similarly in rabbits, lost all animals in little more than 2 months from hydronephrosis, which was produced by obstructing "urinary deposits." French surgeons have had better results with polyethylene tubes in dogs; some have survived as long as 187 days.[5] When some of the latter animals were sacrificed, less than 6 months after replacement of the ureters, normal renal anatomy was found and described. American investigators have had conflicting results. Scher, Erickson, and Scher[19] replaced segments of the ureter with polyethylene tubing in 4 dogs. Three were alive more than a year later, but no pyelographic evidence of function was supplied with their report. How these last investigators prevented migration is not mentioned in the published paper, but it evidently was no problem in their hands. Hardin,[8] using the same material in dogs but replacing the entire ureter, observed encrustation or migration in all of 6 animals. No dog in his series sugvived so long as 6 months. Hardin described a variety of flanging by heat, but it was apparently not sufficient to prevent migration.

The technique we have described, when applied to a superior material, that is, one absolutely resistant to urinary encrustation, may lead to ultimate success in the practical pursuit of a satisfactory ureteral substitute. Additional experiments with Teflon are being conducted with that objective in mind. These present experiments have shown the value of a snug-fitting tube in the gap between renal pelvis and bladder. Prolapse of the prosthesis in either direction can lead to occlusion, hydronephrosis, and death.

SUMMARY

Experience with a doubly-flanged polyvinyl substitute for the dog ureter is described. Of 10 animals used, 3 (two with total bilateral replacement) have survived for more than one year. The flanging technique has prevented migration, but encrustation occurred in one animal. Since the dog ureter is known to encrust less than the human, this experiment demonstrates that: (1) the technique is practical and sound but (2) the material is unsuited for similar therapeutic use in humans.

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A TECHNIQUE OF OPERATING UPON THE FETUS OF THE RABBIT

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INTRODUCTION

REPORTS of experimental operations on the living fetuses of animals usually have placed emphasis upon the difficulties. Therefore, it seems worth while to report that we have not encountered serious difficulties with such operations on rabbits.

In a study of the etiology of congenital muscular torticollis, a series of animal experiments are in progress to investigate the significance of an abnormal intrauterine position in promoting ischemia of the sternomastoid muscle.

Previous experimenters who have operated upon fetuses employed three types of operation. In the first type, the fetus was brought into the abdomen for experimentation then left there as an extrauterine pregnancy.[7] In the second type, the fetus was exposed within the uterus.[1, 2, 4, 6] Usually only destructive procedures were done, although Barnard demonstrated that ileal vessels in the fetus of a dog could be ligated successfully. In the third type, Jost[5] allowed the caudal half of the fetus of a rabbit to emerge for experimentation and then returned it to the uterus. Contrary to our findings, he experienced great difficulty in accomplishing the return, and only succeeded after using antispasmodics. After castrating rabbit fetuses of 19 to 24 days' gestation, Jost reported a 56 per cent survival at the twenty-sixth to twenty-eighth day of gestation when the experiment was terminated.

METHOD

Before the method is described its simplicity is emphasized. There is no doubt that our procedure is simple and that it can be easily adapted to other experimental work of this kind.

After an intraperitoneal injection of Nembutal (15 mg. per pound of body weight) as premedication to a pregnant rabbit, open ether anesthesia is used during the operation. With the animal lying on its back the abdominal hair is clipped; the area is cleansed with Zephiran and draped with sterile towels. A midline incision, extending from the level of the last pair of nipples to just inferior to the umbilicus, is continued through the linea alba and peritoneum.

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When the abdomen has been explored to determine the number and the size of the fetuses present, the free end of one horn is delivered through the wound. Usually the position of a fetus is easily determined by inspection and palpation and its head identified by its shape, size, and firmness. It is important to note that almost always the placenta is attached to the mesenteric side of the uterus and that the antimesenteric wall is relatively avascular. Accordingly, that wall is gripped lightly by two mosquito artery forceps applied along the long axis of the uterus, over the head of the terminal fetus and approximately one-half to three-fourths inch apart. An incision is made lengthwise between the forceps with iridectomy scissors.

No effort is made to preserve the amnionic fluid while the membranes lining the uterus and covering the fetus are being incised. The entire fetus (or preferably the head and shoulders for our experiment) is delivered through the incision. In our particular operative procedure, a 3-0 chromic gut suture with an atraumatic needle is placed first through the scapula then through the upper part of the nose in such a manner that, on tightening it the shoulder and side of the neck are pressed together.

The fetus is returned to the uterus by gentle steady pressure while the edges of the incision are held open by the artery forceps. It is remarkable that during the entire procedure the uterus remains collapsed with little, if any, reduction in size. As a result we have found it easy to return the fetus to the uterus. To close the uterus, one continuous 3-0 chromic gut suture is used. No special care is taken to suture the membranes. Before the abdomen is closed the operation may be repeated on the terminal fetus of the other horn. Peritoneum and linea alba are sutured as one layer with continuous 2-0 chromic gut; the skin is sutured separately with the same size of gut. Penicillin (100,000 units) is injected intramuscularly immediately after the operation.

RESULTS

Operations have been performed on 12 pregnant rabbits between the twentieth and twenty-ninth day of gestation and 14 fetuses have been treated. Six of these mothers have had normal deliveries at term and have produced normal-sized live young.

Most of the possible complications have been encountered. One mother, operated upon on the twenty-sixth day, aborted on the twenty-seventh day, presumably because one of the treated fetuses had died. Two bled to death, one because of a partially detached placenta at the time of operation and the other for reasons unknown. One rabbit had to have a partial hysterectomy because of a detaching placenta during the operation. This rabbit ruptured its uterus at the time of delivery. One mother developed an incisional hernia at the beginning of labor and gave birth to dead fetuses 2 days later. One died from a respiratory infection. The two instances of detached placenta were the only ones encountered.

Some difficulty is being met after birth because of maternal destruction and neglect of the young. Although improved postnatal care has given better

results, it is apparent that the most serious problems lie in the postdelivery period.

SUMMARY

A method of experimentation on the fetus of the rabbit is described. A fetus is totally or partially removed from the uterus for the experiment and then returned. The pregnancy is allowed to continue to term and the young are born without difficulty. During an initial series, in which we have had 50 per cent operative success, a technically simple procedure has been developed.

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Pediatric Surgery

CONDUCTED BY MARK M. RAVITCH, M.D.

AN UNUSUAL DIAGNOSTIC SIGN IN MECONIUM PERITONITIS: VAGINAL DRAINAGE OF MECONIUM

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THE first successful operation for meconium peritonitis was reported by Agerty and associates in 1943. In the intervening 15 years less than 50 cases have been reported. Meconium peritonitis is a sterile chemical and foreign-body reaction resulting from the presence of bowel content in the peritoneal cavity during late intrauterine or early neonatal life. Perforation of the intestinal tract with the resulting peritonitis from meconium can occur from (1) congenital obstruction with perforation, (2) acquired obstruction with perforation, (3) traumatic perforation without obstruction, or (4) several cases have been reported in which there was no evidence of obstruction or of perforation. In this latter group the opening in the intestine has healed so completely that the site is not recognizable.

Those cases which are accompanied by meconium *ileus* will almost invariably show an associated cystic fibrosis of the pancreas with the accompanying mucoviscoidosis so characteristic of this disease.[2, 7] There have been a number of cases of meconium *peritonitis* reported in which there was no evidence of pancreatic dysfunction.

As in many types of congenital intestinal obstruction, the infants are often born of mothers with hydramnios,[1, 5, 6] and in a few cases this finding alone has led to antepartum x-ray studies which have shown the typical x-ray evidences of meconium peritonitis in the unborn infant.[3, 8] This is one of the very few conditions in which the diagnosis can be correctly made before the infant is born.

The physical findings in meconium peritonitis include distention and vomiting, often of bile-stained material. Listlessness and varying degrees of cyanosis or dyspnea may be noted. The infants often do not have audible peristalsis. The abdomen is usually tympanitic and the veins of the abdominal wall may be distended. In the presence of obstruction no meconium stools will be passed.

The most important and pathognomonic finding is seen on ordinary radiographic examination of the abdomen. Neuhauser has demonstrated that no other condition will produce the irregular shadows of calcium scattered within

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the bowel or on the serosal surfaces of the bowel or peritoneum.[4, 9] This appearance is so typical that it has permitted the diagnosis of meconium peritonitis before the birth of the infant. In some reported cases these radiographic signs have been seen and the diagnosis made in an infant who was not operated upon because there was no evidence of persistent intestinal leakage or of obstruction.[2]

In a very few cases it has been possible to see free air in the peritoneal cavity. Once the infant has begun to swallow air it is only a question of time until the sterile meconium peritonitis will become a septic one from the swallowed bacteria if a persistent intestinal leak is present.

There are no radiographic or physical signs of the mucoviscoidosis sufficiently typical to make it possible to diagnose cystic fibrosis of the pancreas at this very early age. The characteristic changes in the sweat and sodium chloride metabolism are not sufficiently well defined to be entirely reliable in the very early neonatal period. In cases of meconium peritonitis due to rupture of the bowel in meconium ileus, the ultimate prognosis is uncertain.

It is well known that the uterus of a newborn female infant is larger than it will be for the next several months as a result of the stimulation of it by the circulating hormones of the mother during intrauterine life. In our search of the literature we could find no previously reported example of the findings reported in the present case as indicative of meconium peritonitis in the newborn female; namely, passage of meconium through the vagina in the absence of a rectovaginal fistula.

CASE REPORT

E. C., a 6-pound girl, was born July 25, 1958, of a mother whose only complication of the pregnancy was development of hydramnios in the few weeks preceding delivery. This was the sixth child of this family. All of the other 5 are living and considered normal. The obstetrician (K. L. C.) noted at the delivery that the amniotic fluid seemed darker in color than normal. At the initial examination of the infant immediately after birth (W. R. M.), the abdomen was noted to be distended and tympanitic and meconium was seen coming from the vagina. On rectal examination the lumen was small and seemed to end blindly at about the 1½ inch level, at which point a tiny plug of hard, grayish meconium could be obtained. Surgical consultation was requested (W. F. P.) regarding the possibility of a small rectovaginal fistula with a high rectal stenosis or atresia. Careful examination showed no evidence of rectovaginal fistula. Material instilled into the rectum did not come out through the vagina, nor the reverse. With a cotton applicator in the vagina it could be determined that the rectovaginal septum was intact and the perineal body normal. It was felt at this examination that the meconium-stained material coming from the vagina represented amniotic fluid trapped in the vagina and expressed after delivery by the baby's cry and the rectal manipulations.

During the next 3 hours it became apparent that there was a persistent discharge of meconium from the vagina and the infant began to vomit bile-stained material. A radiograph of the abdomen was taken and showed some minute areas of flocculent calcification scattered throughout the abdomen. In retrospect it was noted that a tiny rim of free air could be seen beneath the diaphragm on the right. The chest was clear to radiologic and physical examination.

Two tiny plugs of hard, gray meconium were obtained from the rectum on repeated examinations, as noted. The progressive signs of obstruction and peritonitis led to operative intervention at the age of 8 hours.

After introduction of a polyethylene cannula into the saphenous vein at the ankle the abdomen was entered under inhalation anesthesia. The peritoneum was exposed through a right paramedian incision after tying off the cord stump to remove the large mechanical cord clamp applied at birth. The peritoneum was clearly identified but entering it proved to be a difficult matter.

The plastic inflammatory reaction engendered by the extensive meconium soiling proved to be maximal in the right lower quadrant and the bowel wall was so intimately adherent to it at that point that no part of the peritoneum in the right lower quadrant could be freed sufficiently to gain free access to the peritoneal cavity. The rectus muscle was retracted further and the incision extended upward and the free peritoneal cavity entered at a point more distant from the principal point of soiling and intestinal adhesion to the abdominal wall. The abdomen to the right of the midline was full of free, markedly thickened meconium, and in the course of the dissection the uterus and the right tube were finally identified with the fimbriated end of the tube lying free in the middle of the meconium mass. The terminal ileum was distended and obstructed by inspissated meconium down to the ileocecal valve. There was a perforation about 2 cm. in diameter about 5 cm. proximal to the valve.

There was no stenosis, constriction, or atresia. The ileum proximal to that point was moderately distended and there was a marked peritoneal exudative reaction over all of the serosal surfaces of the bowel trapped in the involved area. After the bulk of the meconium had been removed manually and by suction and irrigation, the ruptured bowel was resected together with the most markedly inflamed adjacent segment. The meconium plugs were removed from the ileum to free the lumen into the colon and the patency of this was demonstrated by irrigation with saline solution through to the rectum. No effort was made to irrigate the Fallopian tube or uterus. An end-to-end anastomosis was accomplished using a single layer of 4-0 silk, and the defect in the mesentery was closed with a few sutures of the same material. Because of the physiologic polycythemia and the relatively minor blood loss, the baby required no blood but received some parenteral glucose in water.

Postoperatively the infant was placed on suction for the first 3 days and received parenteral fluids to maintain its caloric, fluid, and electrolyte requirements. The baby continued to pass meconium-stained material through the vagina for 2 days and then a clear watery mucus for another 2 days, and since then has had no further vaginal drainage. The tube was removed on the fourth postoperative day and oral nutrition started. The cutdown was removed the same day. It was possible thereafter to maintain the infant on oral feedings entirely until the twelfth postoperative day. A severe diarrhea developed which persisted to the twenty-fifth postoperative day. During this time she required parenteral fluids to meet the fluid losses from the stools. The infant received pancreatic supplements from the earliest feedings. She was discharged from the hospital on Aug. 29, 1958, having regained her birth weight. The diarrhea had stopped and the infant was taking oral feedings well. Approximately 2 weeks later the infant had to be admitted to the Los Angeles Children's Hospital for management of further intestinal and pulmonary problems due to the fibrocystic disease of the pancreas. She died at the age of 3 months from intractable infection. Autopsy revealed bronchopneumonia and abscesses of the spleen, kidneys, and liver. The operative area was intact.

SUMMARY

A case of meconium peritonitis is reported in which the passage of meconium through the Fallopian tube, uterus, and vagina heralded the presence of free meconium in the peritoneal cavity. This sign has not previously been described. The infant survived the operative correction but ultimately died of uncontrollable infection in association with the fibrocystic disease of the pancreas.

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Announcement

On Feb. 10, 1959, the Buffalo Surgical Society will sponsor the Roswell Park Lecture, this year to be given by Dr. Michael DeBakey, Professor of Surgery and Chairman of the Department of Surgery, Baylor University College of Medicine.

The title of this year's lecture will be "Some Observations on Aortic and Arterial Surgery."

Dr. DeBakey will be awarded the Society's Gold Medal being given for the twelfth time in honor of Dr. Roswell Park, Professor of Surgery, University of Buffalo, 1883-1914. Previous lecturers and recipients of the medal are as follows: Dr. Allen O. Whipple (1948), Dr. Evarts A. Graham (1949), Dr. Dallas B. Phemister (1950), Dr. Frederick A. Coller (1951), Dr. Edward D. Churchill (1952), Dr. Warren H. Cole (1953), Dr. I. S. Ravdin (1954), Dr. Alfred Blalock (1955), Dr. Robert E. Gross (1956), Dr. Alton Ochsner (1957), and Dr. Richard B. Cattell (1958).

COLON MALFORMATION WITH IMPERFORATE ANUS

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Toronto, Ontario

(From the Department of Surgery, the Hospital for Sick Children, and the University of Toronto)

AT THE Hospital for Sick Children, Toronto, a number of cases have been encountered in which newborn infants, presenting with an imperforate anus, had unusual anomalies of the colon. These anomalies were characterized by absence of at least the left half of the colon together with a saccular dilatation of part or all of the remaining large bowel. The dilated segment of bowel was frequently in intimate contact with the urinary bladder. There was often a fistulous connection to bladder or vagina.

Congenital malformations of the rectum and anus are said to occur once in every 1,500 to 5,000 births.[2] In the most common and extensive form (Type III, Ladd[4]), the rectum is partially or completely absent, but the sigmoid colon is intact. Colon anomalies are not usually considered a part of this malformation.

Colon atresias are much less common, occurring about once in every 15,000 to 30,000 births.[7] These appear in two forms, an internal diaphragm or an absent segment of bowel, and are usually associated with a normal anus and rectum. The absent segment is generally short, but rare cases involving longer portions of colon have been reported.[1, 3, 6] The only case that we have been able to find similar to our cases was reported by Spriggs in 1912.[5] He described a pathologic specimen (London Hospital Museum, 1882) with an imperforate anus and absence of the left colon. The ileum, cecum, and appendix were distended.

CASE REPORTS

Case 1.—B. R., an 8 pound 12 ounce white boy, was admitted shortly after birth on Nov. 13, 1941, for treatment of cerebral trauma and an imperforate anus. The infant died when he was 24 hours old and a postmortem examination was performed.

The abdomen was tensely distended by a large saclike segment of colon which measured 15 by 10 by 8 cm. and overflowed the whole left half of the peritoneal cavity (Fig. 1). The cecum and appendix were in the right lower quadrant, but the ileum approached the cecum from above and to the right. The cecum was tilted to the left where it entered the large blind sac of colon. The latter was filled with air and thick greenish mucoid material. It was closely adherent below to the posterior surface of the urinary bladder and communicated with it by means of a small fistulous opening. There was no other remnant of colon or rectum.

The infant was also noted to have Meckel's diverticulum, hypospadias, undescended testicles, early hydronephrosis, and signs of central nervous system trauma.

Case 2.—R. S., a 5 pound Negro girl, was admitted on Sept. 27, 1949, at one day of age. She had an imperforate anus and a history of passing greenish material by vagina.

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Her general condition was quite good and there was no abdominal distention. Roentgenograms revealed a large dilated segment of bowel lying just above the bladder. Wangensteen-Rice views showed no air-containing bowel in the pelvis. On the posterior wall of the vagina there was a high fistulous communication, which decompressed the intestinal tract adequately. The child was subsequently discharged without operation.

At intervals over the next 6 years the colovaginal fistula was dilated, and on one occasion a colostomy was constructed but failed to function satisfactorily.

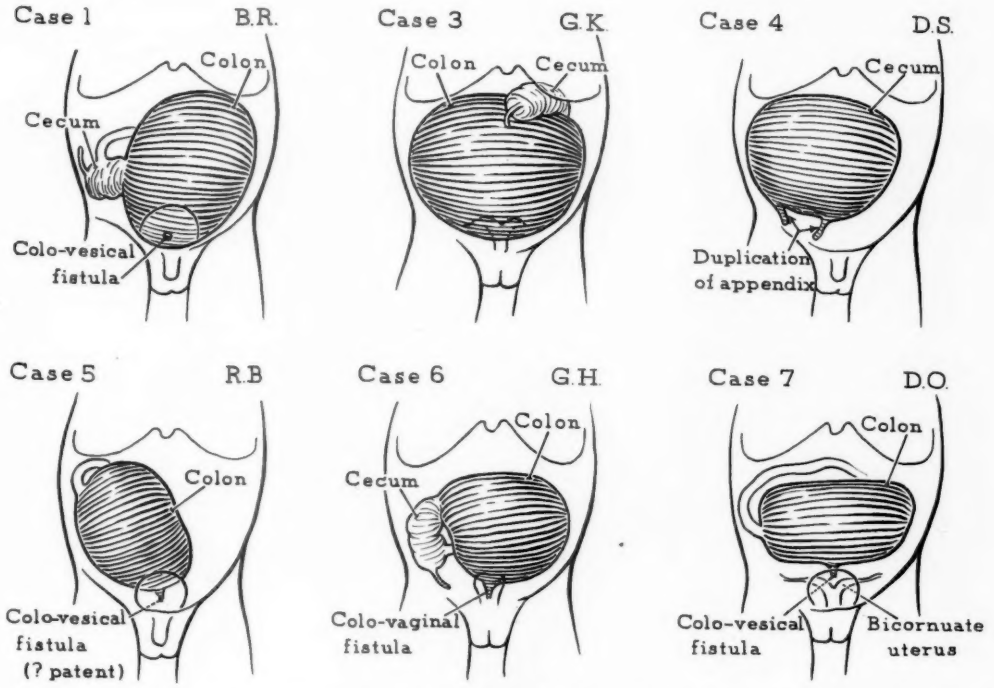

Fig. 1.—Graphic representation of the colon deformity in 6 cases. Cases 4, 5, and 7 are similar in that a single large saclike structure is the only apparent remnant of large bowel. Cases 1, 3, and 6 possess a cecum as well.

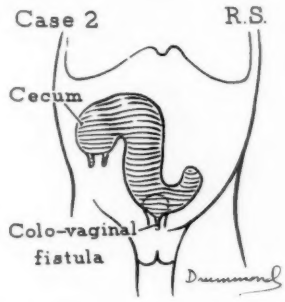

Fig. 2.—Drawing of colon malformation noted in Case 2 at 6 years of age.

On Sept. 15, 1955, when the child was 6 years old, she was subjected to a careful laparotomy (Fig. 2). The cecum, although normally situated, possessed two appendices. A short length of ascending colon approached the right upper quadrant, then turned acutely backward and downward to enter the pelvis, where it communicated with the vagina. From this point, there was a short stubby projection of colon anteriorly, just above the bladder. The total length of the colon was approximately 20 cm. After closing the colovaginal fistula, the colon distal to it was excised and the proximal end brought out in the right lower quadrant as a colostomy. The appendices were excised.

Recurrent stenosis and obstruction necessitated revision of the colostomy in October, 1957. At that time a further 5 cm. of colon was excised, thus leaving only 10 cm. of large bowel. Nevertheless, the child has maintained good health and reasonable development. At present her colostomy is functioning well with 4 semiformed movements daily.

CASE 3.—G. K., a 5 pound 13 ounce white girl, was admitted on Dec. 12, 1950, at one day of age for treatment of an imperforate anus. Her abdomen was markedly distended and tympanitic. There was no demonstrable external anal sphincter or dimple. Roentgenograms revealed a massive globular loop of bowel, distended with fluid and air and almost filling the whole abdominal cavity (Fig. 3). The remaining loops of bowel were displaced into the upper abdomen.

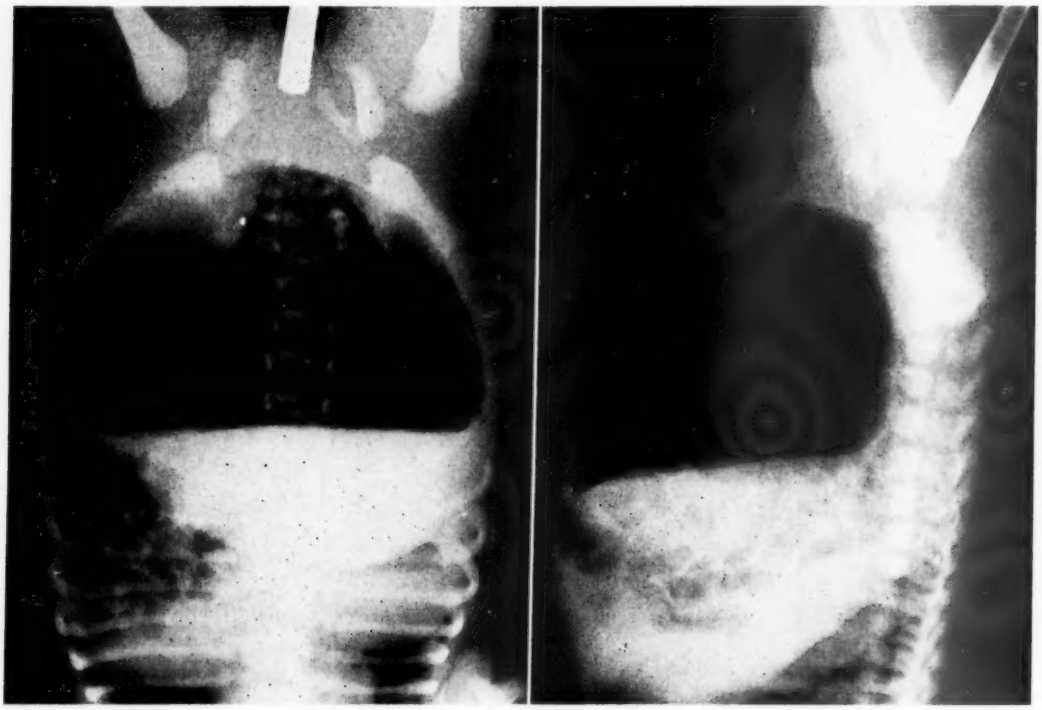

Fig. 3.—Wangensteen-Rice views of Case 3 at one day of age. The massive segment of colon almost fills the abdominal cavity.

At operation later that day, proper abdominal exploration could not be achieved until this huge cystlike mass was collapsed by aspiration with a fine needle and syringe. The cecum and appendix lay in the left upper quadrant and communicated with this structure. There was no other segment of colon or rectum. A colostomy was fashioned in the left lower quadrant with the dilated colon.

Three days after the operation, the child died in anuria. Postmortem examination revealed the large bowel to be only 15 cm. in length. Although there was intimate contact with the posterior aspect of the bladder distally, there was no fistulous communication. A number of congenital genitourinary defects were noted: bilateral hydronephrosis and hydroureter, bicornuate uterus, and a vesicovaginal fistula.

CASE 4.—D. S., a 7 pound 10 ounce white boy, was admitted on July 23, 1953, at one day of age, with an imperforate anus. Despite a moderately tense distended abdomen, his general condition was good. Other congenital anomalies noted during his stay in the hospital were: right talipes equinovarus, right undescended testicle, perineal hypospadias, and right hydronephrosis and hydroureter.

Roentgenograms on admission revealed a large segment of bowel, distended with air and fluid, almost filling the lower abdomen (Fig. 4). There was also radiographic evidence of a small right pneumothorax and a congenital defect of the lower lumbar spine and sacrum.

At laparotomy on the day of admission, the greatly distended segment of bowel appeared to be a huge cecum which ended blindly to the left of the midline. It possessed two vermiform appendices. Its blood supply was anomalous in that it was derived from many small vessels. In freeing the cecum, an area of cyanosis developed over its inferior border. This portion was excised and the balance was used to construct a right lower quadrant colostomy.

Three days later the colostomy was opened. The child progressed well postoperatively and was discharged on the sixteenth day. Subsequently, this case was lost to follow-up but is believed to have died of genitourinary disease several months after discharge.

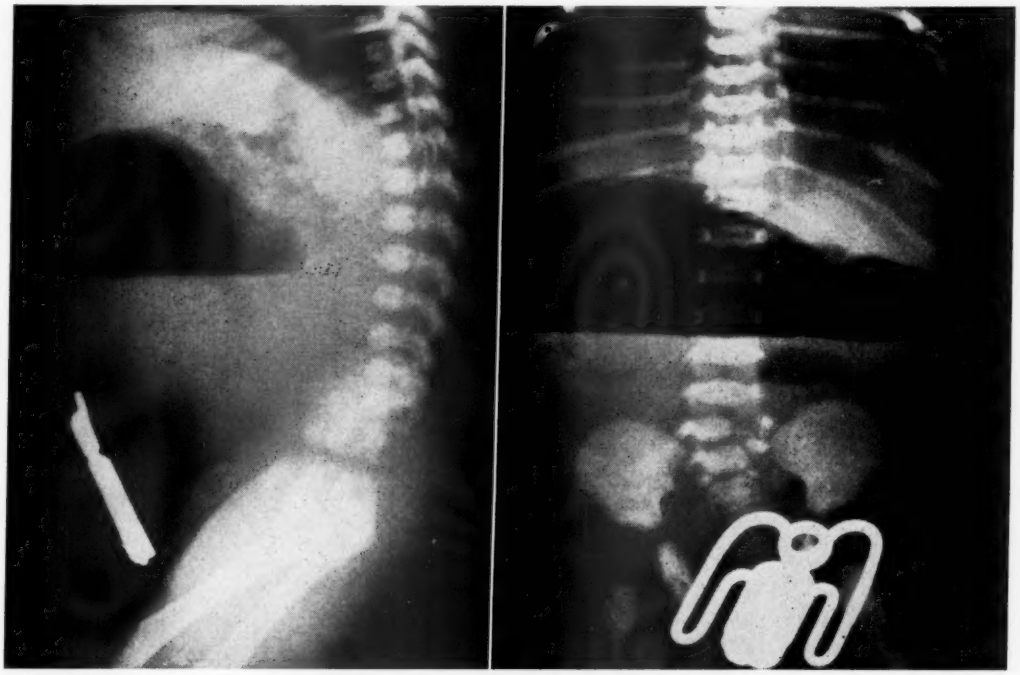

Fig. 4.—Upright roentgenograms in Case 4 indicate the huge size of the saclike colon.

CASE 5.—R. B., an 8 pound white boy, was admitted on the day of birth, Jan. 23, 1956, for treatment of an imperforate anus. Apart from moderate abdominal distention, the child's general condition was satisfactory. In the anal area there was dimpling and active puckering of the skin. Roentgenograms showed a globular, distended segment of bowel, displacing the other abdominal viscera.

Abdominal exploration was carried out when the child was 24 hours of age. The globular segment of bowel seen radiographically was approximately 9 cm. in diameter and was the only remnant of large bowel which could be found. The ileum entered on its right superior aspect. It was adherent to bladder inferiorly and when dissected free was found to send a small prolongation to the bladder neck area. This was ligated and divided, but its complete patency was never determined. In the right paraumbilical region a colostomy was fashioned with the base of this prolongation.

A troubled postoperative course ensued, with frequent diarrhea, vomiting, and a wound infection. Before his eventual discharge on March 28, 1956, it was necessary to revise the colostomy. Stenosis and obstruction at the colostomy site recurred and finally, at 10 months of age, the segment of colon was excised leaving an ileostomy. Since then, the ileostomy has functioned very well with 4 or 5 semiformed stools daily. The child has gained and developed as a normal infant.

CASE 6.—G. H., a 5 pound 14 ounce white girl, was admitted on June 7, 1957, at one day of age, with abdominal distention, vomiting, and an imperforate anus. Roentgenograms demonstrated a large loop of distended bowel occupying most of the lower abdomen; the rest of the bowel was displaced superiorly. Gas and fecal material were passed by vagina. This fistula failed to maintain reasonable intestinal decompression so that operation was considered necessary.

Laparotomy one week after admission found the bowel matted with dense old adhesions indicative of an antepartum peritonitis. The terminal ileum cecum, and appendix lay in the right lower quadrant. The cecum was 3 cm. in diameter, and joined the large saccular segment of colon which had been noted radiologically. This portion of colon measured 10 by 6 by 6 cm., and it possessed a fistulous communication with the genitourinary system inferiorly. The fistula appeared to enter the vagina immediately behind the bladder. The fistula was divided and oversewed, while the colon and cecum were excised and an ileostomy was constructed.

The child died rather suddenly one week after operation, presumably due to an electrolyte imbalance. At autopsy, a double uterus and vagina were found, with the two vaginas entering a short cloacal chamber just posterior to the sutured fistulous tract and the urinary bladder. Furthermore, in the pelvis, where one would expect to find a rectum, there was a closed tubelike structure measuring 6 cm. in length and 3 cm. in diameter.

CASE 7.—D. O., a 7 pound 4 ounce white girl, was admitted, shortly after birth on June 23, 1957, vomiting bile and showing increased abdominal distention. She had an imperforate anus with no sign of an external anal sphincter. Roentgenograms (Fig. 5) showed a large dilated segment of bowel with air-fluid levels. On Wangensteen-Rice views, the gas appeared to pass to within 5 mm. of the marker, but this was considered to represent air in the bladder.

Laparotomy displayed a tremendous dilatation of the colon (12 by 6 cm.). There was no appendix and no other remnant of large bowel. Inferiorly, a fistulous extension, 1 cm. in diameter, led from the colon down between two horns of a bicornuate uterus to enter the bladder close to its neck. Part of the blood supply to the colic sac arose from the greater omentum and this was carefully preserved. The fistula was divided between clamps and then oversewed. Part of the wall of the colon was brought out through an incision in the left lower quadrant to form a colostomy.

The child's postoperative course was uncomplicated. Following discharge on July 16, 1957, she continued to gain weight and develop normally. The colostomy functioned well with about 6 pasty semiformed stools daily. A barium enema at 9 months of age revealed that the globular colon had changed little in size and contained a large amount of fecal material (Fig. 6).

DISCUSSION

It was surprising to find that in the hospital records this unusual colon anomaly had occurred more frequently than straightforward colon atresias, of which we had encountered only one proved case. In the period from 1924 through 1957, there were 271 cases of imperforate anus treated at this hospital. The 7 cases herein presented therefore represent an incidence of about 2.5 per cent.

Five of the 7 cases exhibited multiple congenital defects, thus suggesting that this lesion resulted from an early or extensive error in the development of the fetus. Four children failed to survive. Two died from associated anomalies or disease. The third was reported to have died secondary to a genitourinary defect, and the fourth from electrolyte imbalance.

This anomaly appears to be essentially an absence of the hind-gut with some malformation of the terminal portion of the mid-gut. This malformation

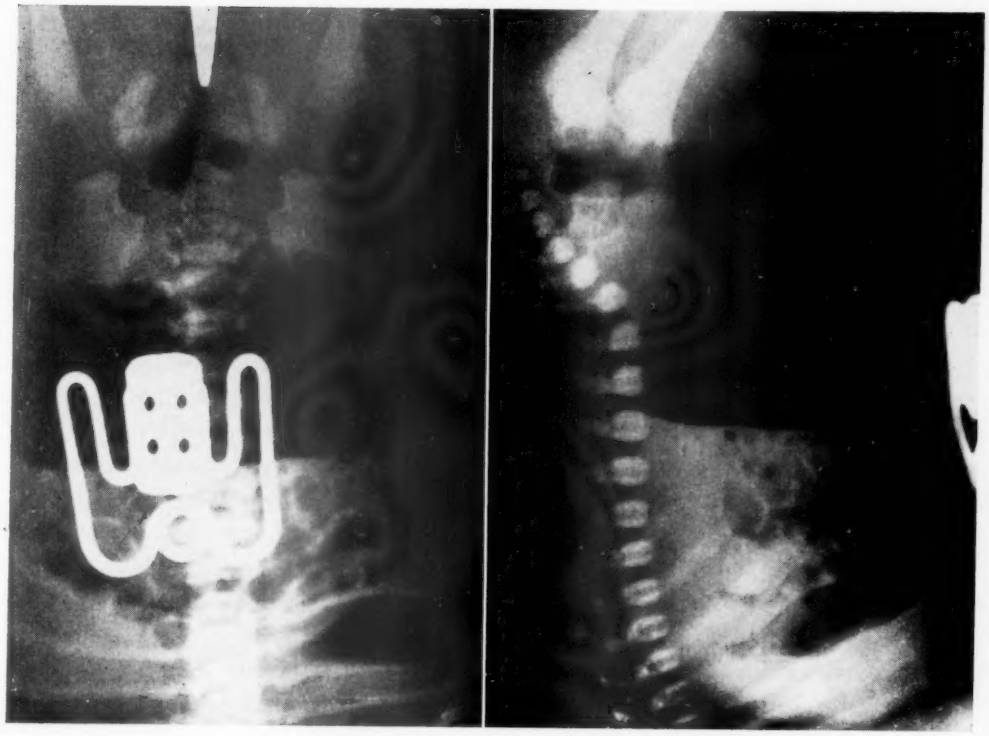

Fig. 5.—Wangensteen-Rice views of Case 7 show a large dilated segment of colon with air-fluid levels. Through a colovesical fistula, gas has entered the urinary bladder.

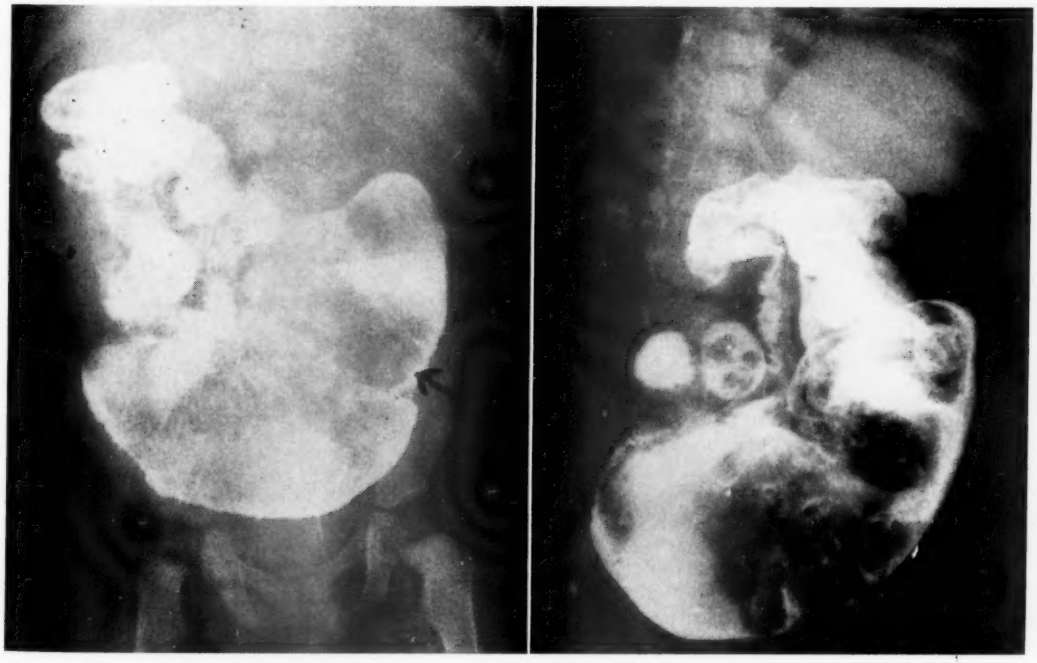

Fig. 6.—Case 7. Barium enema at 9 months of age reveals little change in the size of the colon. Retained fecal material suggests poor motor function with inadequate emptying. The arrow points to the colostomy opening

is undoubtedly influenced by the chronic obstruction and distention present in utero. In Cases 4, 5, and 7, the anomaly was remarkably similar, with a single globular sac of colon the only apparent remnant of large bowel. Evidence of duplication was noted in 2 cases. It is of interest that in Case 6 a small closed tubelike structure was found in the posterior pelvis, as if representing the rectum. In 5 of the 7 cases there was a fistula between the enlarged segment of colon and the bladder or vagina. Colon sections were examined microscopically in 5 cases and normal ganglion cells were present.

When, in a newborn child with imperforate anus, this colon anomaly is found, early laparotomy and colostomy are usually necessary. Because of its absorptive function, preservation of a maximum amount of large bowel is preferred in the early months of life. However, experience has shown that these saclike segments of bowel fail to decrease in size to any major extent and therefore possess poor motor function. This leads to retention of feces with stenosis and stricture of the colostomy stoma. Recurrent failure of the colostomy has necessitated revisions in 2 of the 3 survivors. One patient (Case 2) is now left with only a small amount of colon, and the other (Case 5) has a very satisfactory ileostomy. The third living patient (Case 7) is too recent to assess completely but already shows poor emptying of the large bowel segment, with retention of feces.

Although untried, it is possible that a plastic procedure converting the sac of large bowel into a longer narrower tubular structure might result in improved motor function and emptying. If this worked well, perhaps it could be anastomosed to the anus by an abdominal perineal "pull-through" procedure. A major difficulty then might be the blood supply which in 2 cases was at least partially anomalous in origin.

SUMMARY

Of 271 patients with imperforate anus, 7 are reported exhibiting a rare colon anomaly characterized by absence of the left colon plus saccular dilatation of part or all of the remaining colon. In 3 patients, the only remnant of large bowel was a single large saccular structure. Fistulous connections with the genitourinary system were present in 5 patients.

Early laparotomy with colostomy was usually necessary. Late complications due to poor motor function of the large saccular segments of colon necessitated colostomy revisions in 2 of the 3 surviving patients.

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ACUTE THORACIC EMERGENCIES IN INFANTS AND CHILDREN WITH STAPHYLOCOCCIC PNEUMONIAS

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AN AIR of complacency concerning the appearance of pneumatoceles in the course of staphylococcic pneumonias in infants and children has been engendered by the reports of a number of authors.[1-4] The fallacy of this attitude and the serious consequences of tension pneumothoraces occurring in this group of patients are emphasized in this report of 14 children who have presented this dramatic syndrome.

The sudden occurrence of a tension pneumothorax in a child ill with pneumonia has produced one of the most climatic surgical emergencies with which we have had experience. This complication we believe is due to rupture of an emphysematous lesion. The rapid deterioration it produces can only be counteracted by prompt recognition and treatment if a fatality is to be prevented. The fact that this event may develop when concern is diminished by the apparent clinical control by adequate antimicrobial therapy increases the potential hazard of the lesion.

The fourteen children who form the basis of this report were seen between July, 1955, and July, 1958. There were 9 girls and 5 boys in the group, aged from 5 days to 13 years, with an average age of 2.1 years. All of the patients except one had been considered healthy and normal prior to the acute illness. The one exception mentioned above was a child in whom a tetralogy of Fallot had been recognized since birth. A coagulase positive, hemolytic *Staphylococcus aureus* was isolated as the causative agent in each patient. The disc plate method was utilized for determining in vitro drug susceptibility of the organisms with concentrations in the media of 1.5 units per milliliter of penicillin, 10 mcg. Aureomycin, 10 mcg. Chloromycetin, 10 mcg. erythromycin, 50 mcg. Furadantin, 6 mcg. novobiocin, 10 mcg. streptomycin, 10 mcg. Terramycin, and 10 mcg. tetracycline.

CASE REPORTS

CASE 1.—P. W., a 13-year-old girl with a known tetralogy of Fallot, was admitted to the hospital Aug. 11, 1957. She had had headache and fever of 2 days' duration; dyspnea had appeared about 3 hours prior to hospital admission.

Physical examination revealed a girl in moderate respiratory distress who appeared cyanotic and lethargic. Her temperature was 102° F.; pulse was 110 and respirations 28. The hemoglobin was 18 Gm. per cent, the hematocrit was 66, and the white blood count was 13,900. Coagulase positive staphylococci isolated from throat and blood cultures

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made on August 12 proved to be resistant to penicillin and erythromycin but were sensitive to Chloromycetin, novobiocin, and tetracycline. Roentgenograms on admission showed bilateral pulmonary infiltrates with radiolucent areas (Fig. 1).

In spite of massive antibiotic administration the patient's temperature remained elevated and she appeared acutely ill. On August 16 there was a sudden dramatic deterioration of the patient with marked dyspnea, cyanosis, and depression. The right chest was found to be tympanitic and there was a marked shift of the apex beat to the left axillary line (Fig. 2). An emergency right thoracostomy was performed in the patient's room at a time when she was comatose and appeared moribund. After decompression of the right tension pneumothorax by introduction of a large tube connected to a water-seal drainage system there was dramatic improvement of breathing and a gradual return to the patient's former status (Fig. 3). The right lung re-expanded although a small air leak persisted so that the tube drainage was connected with regulated suction in the system. On August 24 a similar episode of sudden severe dyspnea supervened and the patient expired before any resuscitative measures could be employed.

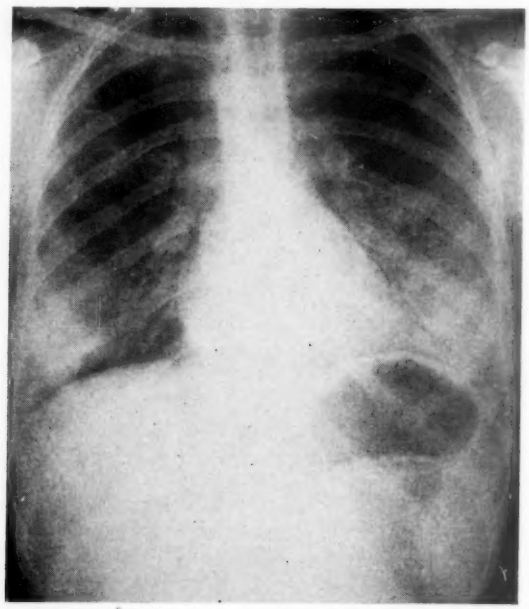


Fig. 1.—Case 1. Posteroanterior roentgenogram on admission showing bilateral lower lung infiltrates and radiolucent areas.

At postmortem examination a left tension pneumothorax was present in addition to a bilateral hemorrhagic pneumonia, pyopneumothoraces with emphysematous bullae and blebs, abscesses, and small pulmonary infarctions. It was found that the cause of the pneumothoraces had been rupture of emphysematous blebs.

CASE 2.—S. K., a 6-month-old infant, was admitted to the hospital on April 15, 1956, because of a respiratory infection of one week's duration and fever up to 103° F. which had persisted for 3 days in spite of penicillin therapy. Examination revealed an acutely ill girl weighing 15 pounds, 8 ounces with a temperature of 104.5° F. The hemoglobin was 11.2 Gm. per cent, the red blood cell count was 4.34 million per cubic millimeter, and the white blood cells 25,200 per cubic millimeter. The patient appeared dry, pale, and listless. The left chest was dull to percussion and the breath sounds were absent on auscultation. A chest x-ray revealed an opaque left chest with a radiolucent area (Fig. 4).

The child's condition did not improve with adequate therapy of penicillin, streptomycin, and Aureomycin. On the thirteenth day after admission the child was found by the ward nurse to be gasping, restless, and pulseless. Seen in emergency consultation, the child's condition appeared preterminal. Outstanding in the physical examination was

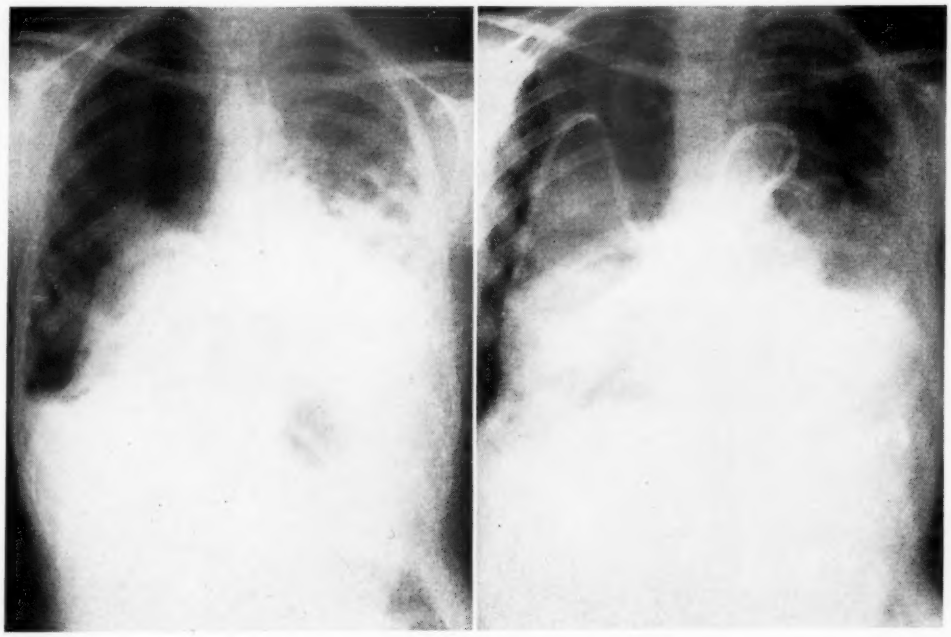
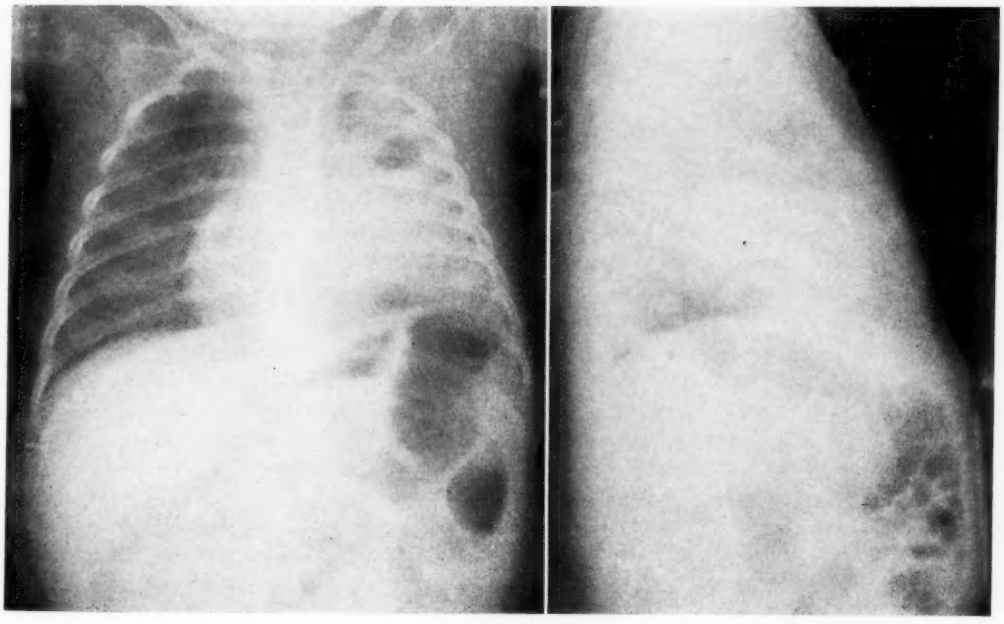


Fig. 2. Fig. 3.

Fig. 2.—Case 1. Emergency roentgenogram demonstrating right tension pneumothorax with associated changes in left lung.

Fig. 3.—Case 1. Roentgenogram taken after placement of thoracostomy tube showing beginning re-expansion of right lung.



A. *B.*

Fig. 4.—Case 2. Roentgenogram of Patient S. K. on admission demonstrating opaque left lung, radiolucent areas in upper lobe.

a marked shift of the apex beat to the right. The left chest had a tympanitic note. A large needle was thrust into the left hemithorax in the second anterior intercostal space with a sudden expulsion of air and fluid. The child's condition improved at once. Thoracostomy was performed and tube drainage of the left chest was instituted.

Coagulase positive, hemolytic *Staphylococcus aureus* was isolated from cultures of the pleural fluid. This strain was sensitive only to erythromycin. The patient was treated with the latter drug and the chest tube was removed in 2 days after apparent expansion of the left lung. Her recovery was prompt and she was discharged to her home 6 days following this critical complication. Follow-up studies and x-rays have shown the patient to be perfectly normal and well (Fig. 5).

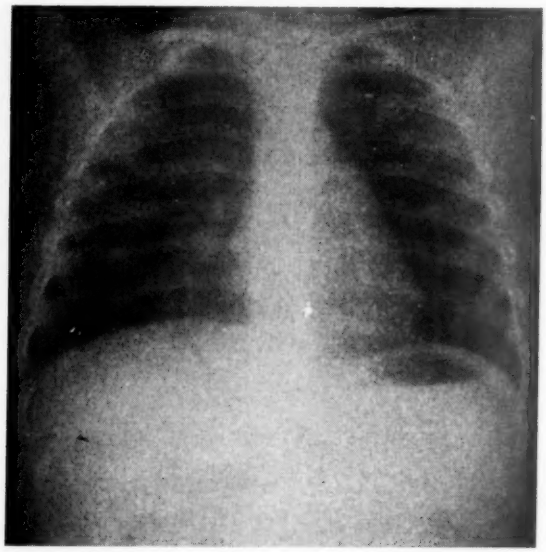


Fig. 5.—Case 2. Roentgenogram taken one month after pneumothorax in course of staphylococcic pneumonia.

CASE 3.—C. G., a 5-month-old girl, was admitted June 22, 1958, because of sudden increasing respiratory distress of 4 hours' duration. She had been treated at home for 6 days for a persistent upper respiratory infection with erythromycin without resolution or improvement. On admission she presented a picture of marked respiratory difficulty, a shift of the apex beat to the left, and a temperature of 103.6° F. Roentgenograms confirmed the presence of a right tension pneumothorax with apparent consolidation of the underlying lung (Fig. 6).

A right thoracotomy was performed under local infiltration anesthesia in the operating room. The right pleural space was opened by an incision in the sixth intercostal space in the mid-axillary line. Air and fluid were expelled under great pressure. A small Fryer tube was inserted into the pleural space and connected to water-seal drainage. Cultures of the pleural fluid yielded coagulase positive staphylococci which were resistant to all antibiotics except Chloromycetin and novobiocin. The child's breathing was markedly improved but did not return completely to normal. Bronchoscopic aspiration removed a large mucous plug from the right bronchus. A polyethylene tube was also inserted into the left greater saphenous vein for the administration of blood and parenteral fluid.

There was gradual improvement of the patient's status under Chloromycetin therapy. Expansion of the right lung appeared to be complete 3 days after thoracostomy, when the pleural tube was removed. The patient was discharged to her home one week after her admission (Fig. 7). She has continued to do well and a follow-up chest film on Aug. 20, 1958, demonstrated no lesion.

Fig. 6.

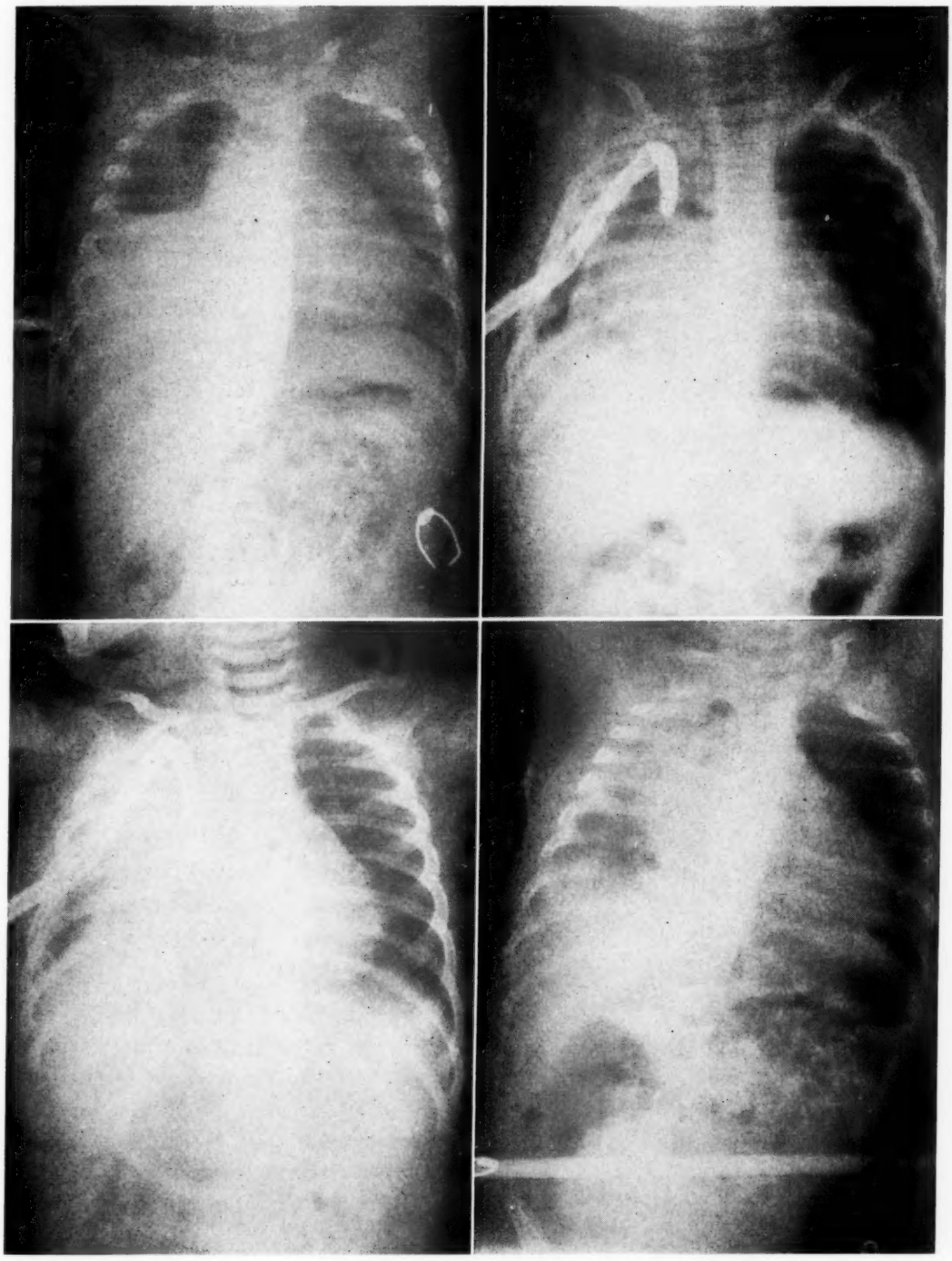


Fig. 7.

Fig. 6.—Case 3. *A*, Admission roentgenogram showing right pyopneumothorax with mediastinal displacement. *B*, After insertion of thoracostomy tube.

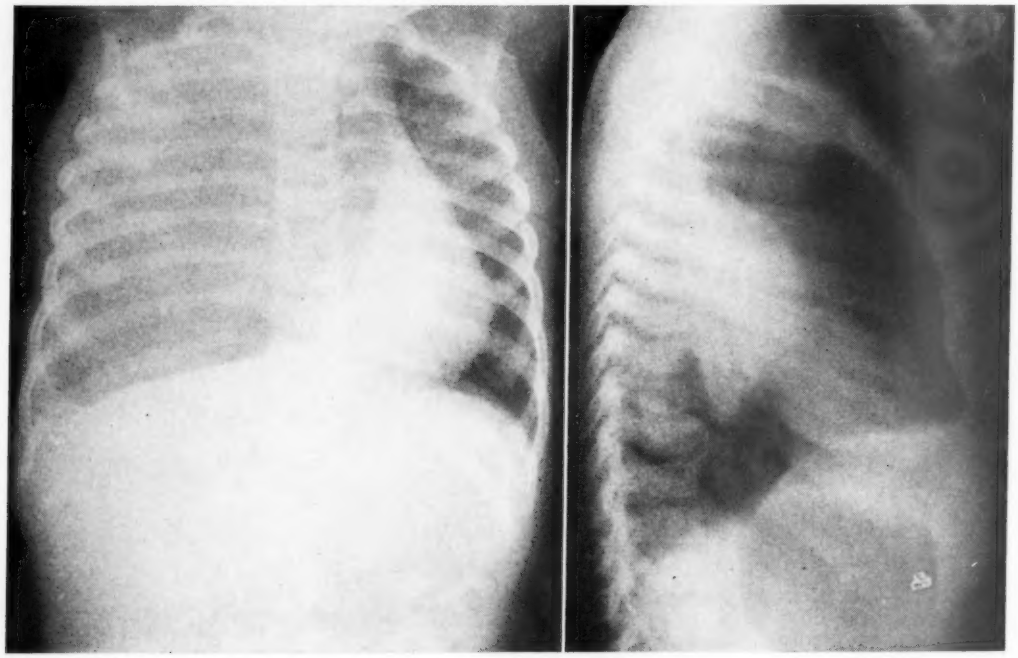
Fig. 7.—Case 3. *A*, Roentgenogram 3 days after thoracostomy. The tube was removed on this day. *B*, Roentgenogram 6 days after thoracostomy.

CASE 4.—J. W., a 16-month-old girl, was admitted June 7, 1958, because of "trouble with breathing" of one day's duration. Three days prior to admission therapy had been begun with a tetracycline drug because of rhinorrhea, cough, and fever.

She was an acutely ill, pale, and pasty infant with moderate respiratory distress. The pharynx was red and edematous. Small cervical lymph nodes were felt. The heartbeat was rapid with a rate of 136. Râles were heard in the left chest and diminished breath sounds were noted over the right thorax. Her temperature was 101° F.

The hemoglobin was 12.5 Gm. per cent; white blood count was 18,350; and urinalysis showed a trace of albumin and the presence of acetone. Throat cultures yielded a coagulase positive, hemolytic *Staphylococcus aureus* which was sensitive only to Chloromycetin, streptomycin, and erythromycin and was resistant to the other common antibiotics. Roentgenograms on admission showed pneumonia on the right and an apparent pneumatocele.

In spite of vigorous antibiotic therapy the child's condition was unaltered until June 10, 1958, when there was a sudden dramatic change in her status with marked respiratory distress and apparent mental depression. The primary change noted on physical examination was a shift of the apex beat to the left. Roentgenograms confirmed the marked shift of the mediastinum toward the left with further compression of the right lung (Fig. 8).



A. *B.*

Fig. 8.—Case 4. Posteroanterior and lateral roentgenograms demonstrating right tension pneumothorax, with striking mediastinal displacement.

An emergency incision in the second anterior intercostal space on the right produced an immediate expulsion of fluid and air under great pressure. A No. 18 Fryer tube was placed in the pleural space for underwater drainage and a tracheal bronchial toilet was performed utilizing a small endobronchial tube and a catheter (Fig. 9). The child's respirations were markedly improved and her lung appeared completely expanded the next day. Cultures of the pleural fluid confirmed the presence of a coagulase positive *Staphylococcus aureus.*

The child's clinical picture improved markedly and the lung expanded readily. Drainage from the chest tube ceased and the tube was removed on June 16, 1958. The roentgenograms continued to show a persistence of radiolucent areas and antibiotic

therapy was continued. There was very little change in the clinical and radiologic picture until July 6 when she became anoretic and a temperature elevation recurred. Diarrhea made its onset on July 8, and her temperature rose to 103° F. Coagulase positive, hemolytic staphylococci resistant to all antibiotics were isolated from stool cultures. In the afternoon of the same day the child had a sudden episode of severe dyspnea and appeared moribund (Fig. 10).

She was returned to the operating room and a second right thoracotomy was performed in the seventh intercostal space in the mid-axillary line. Again there was an escape of fluid and air under great pressure. A small Fryer tube was inserted and connected to underwater drainage (Fig. 11). The child's improvement was again dramatic. The lung expanded rapidly, her temperature returned to normal, and the tube was removed after 4 days. The patient was treated by small transfusions. She was discharged to her home on July 22 where she continued to show clinical improvement. Follow-up examinations and roentgenograms have shown a return to normal.

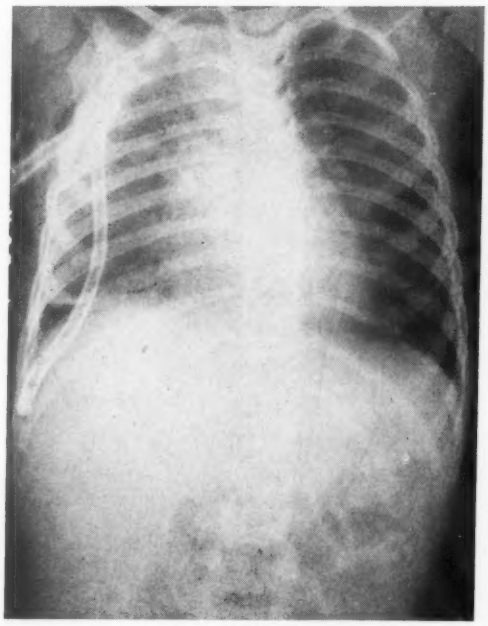


Fig. 9.—Case 4. Appearance following thoracostomy. Note expansion of right lung and radiolucent area at hilum.

DISCUSSION

The patients reported have dramatically demonstrated the impact which complications may cause on the course of acute staphylococcic pneumonia in children and infants. An evaluation of this aspect of the combination of emphysematous disease with pneumonia requires more emphasis and stress as a source of dangerous hazards in respiratory disease.

Infections with the resistant forms of staphylococci have become more protean and prevalent in the past 5 years as has been evident by the increased number of reports of this infection in the literature.[6] The virulence and rapidity of onset in some of the 14 patients described herein was particularly noteworthy. In 9 no bacteriologic diagnosis was made prior to appearance of the pneumothorax; three had no radiologic diagnosis of pulmonary disease before this complication was encountered, and three had only minor respiratory symptoms before recognition of the thoracic catastrophe.

The high incidence of emphysematous cysts in staphylococcic pulmonary infections we have believed due to bronchial disease with consequent acute local obstructive phenomenon.[5] The symptoms of the lesions in this group of patients were due to the apparent tendency to rupture into the open pleural

Fig. 10.

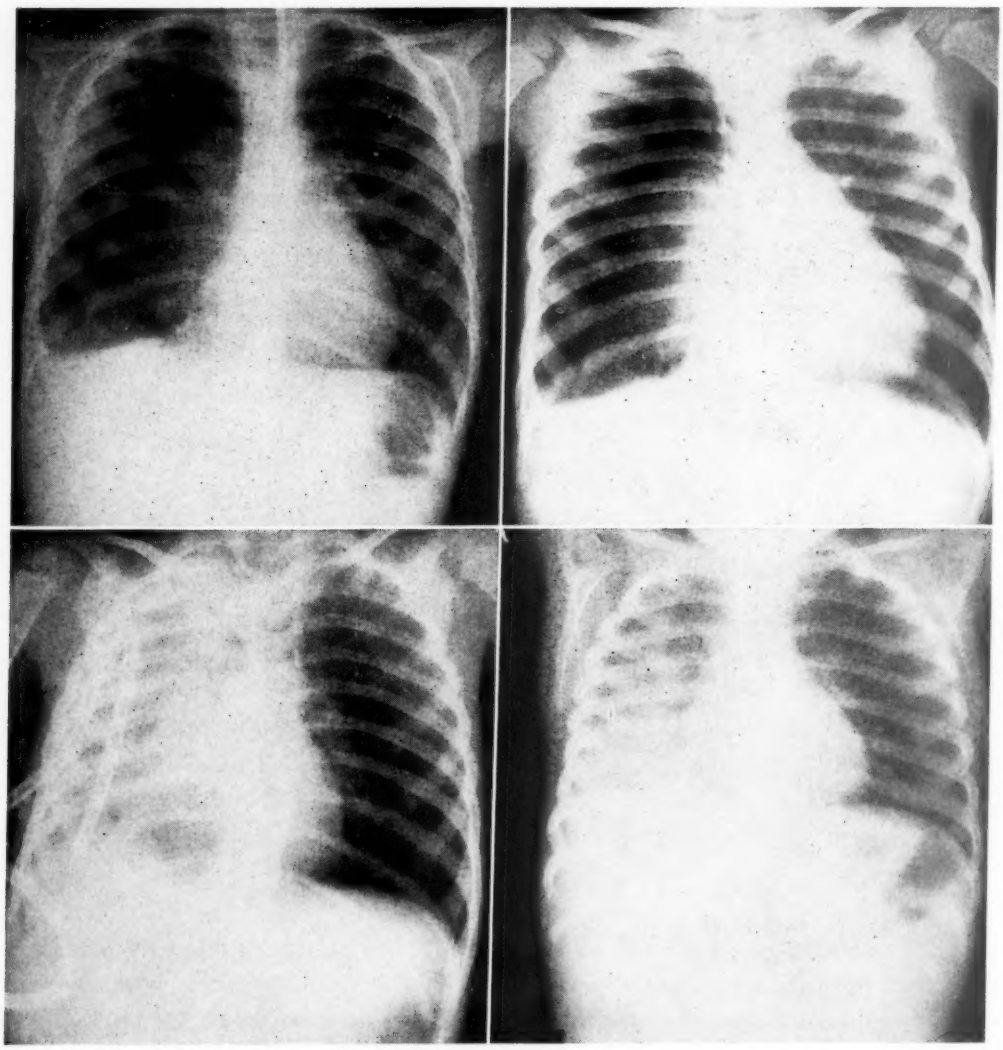


Fig. 11.

Fig. 10.—Case 4. *A*, The radiolucent area at the right hilum is more clearly seen and the pneumothorax has recurred. *B*, The pneumothorax is still more marked and the collapse and shift are greater.

Fig. 11.—Case 4. *A*, Film after second tube thoracostomy. *B*, Film at time of discharge from the hospital. The opacity cleared completely in one month.

space producing the serious pathophysiologic changes illustrated by the case histories included. In addition these lesions may cause lung compression because of their size. Infection of the space may also supervene with secondary abscess formation.

The organisms recovered from these patients were all pathogenic and none could be traced to any specific source of infection by clinical methods. The bacteria in addition demonstrated some resistance to antibiotics, but there was no standard pattern since in each case there was an individual difference in the sensitivity spectrum.

The treatment of tension pneumothorax in these pictures is particularly important in view of the limited pulmonary reserve in infants and small children. The combination of sudden lung collapse with a generalized pulmonary infection and resultant diffusion defects readily explains the severe effect that this ventilatory change produces on the patient's cardiorespiratory mechanism.

The reduction of the pneumothorax by the institution of water-seal pleural drainage was sufficient in all of these patients to cause improvement and recovery in all but one. The one death was due to the sudden development of a contralateral pneumothorax in conjunction with an already impaired cardiorespiratory mechanism due to congenital heart disease. All the other patients recovered, with apparently complete resolution of the pulmonary process.

SUMMARY AND CONCLUSIONS

1. Fourteen patients have been presented with a serious tension pneumothorax complicating staphylococcic pneumonia.

2. The presence of emphysematous lesions in the course of pneumonia demands surgical consultation and preparations for emergency therapy.

3. In serious pneumothoraces of infants and children the possibility of staphylococcal origin should be considered.

Tension pneumothorax is a serious complication of staphylococcal pneumonia in infants and children. In the presence of radiographic demonstration of radiolucent areas in the lungs of children with staphylococcal pneumonia, the possibility of this complication should be considered. Its occurrence requires immediate tube thoracotomy and underwater drainage. Fourteen infants and children are reported who were treated for this complication; thirteen are alive and well. The one death occurred in a child with tetralogy of Fallot who was recovering after catheter thoracostomy for a right tension pneumothorax when she succumbed to a left tension pneumothorax.

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THE DIAGNOSIS AND TREATMENT OF CORONARY ARTERIOVENOUS FISTULA

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CONGENITAL anomalies of the coronary arterial tree are seldom seen and relatively unknown. Recent progress in cardiovascular research clearly demonstrates that these conditions, although rare, have significant clinical importance. The malformation of a coronary artery may develop at its point of origin, in its distribution system, or in its drainage. Clinicians have interest in all the above varieties, but from the therapeutic standpoint only the last group, the abnormal coronary arterial drainage, holds particular importance.

Twenty-one cases of abnormal coronary arterial drainage were found in the literature. Most of the cases were identified as "coronary arteriovenous fistula." However, there are only 6 reported direct communications between the coronary arterial and venous systems. Three anatomic variants were described[1-21]: (1) a coronary artery draining directly into a heart chamber, (2) one of the coronary arteries draining directly into the pulmonary artery, and (3) "true" coronary-venous fistula, that is, direct communication between the coronary arterial and the venous system.

The unusual clinical symptoms and the rarity of these abnormalities are the reasons all of these cases were diagnosed at autopsy, accidentally, or on the operating table.

Four of the reported 21 cases[4, 9, 19, 20] were operated upon successfully, and all of these belong to the first two groups. None in the third group ("true" coronary arteriovenous fistula) were treated surgically.

We should like to present two cases of the arteriovenous fistula type which were operated upon successfully: (1) a child with serious cardiac symptoms and a "true" coronary arteriovenous fistula and (2) an 18-year-old girl with an arteriovenous aneurysm connecting the left coronary artery to the right ventricle.

CASE REPORTS

CASE 1.—A white girl, 4 years old, was admitted on March 10, 1958, for cardiac catheterization. The child was born prematurely. A cardiac murmur was known to exist from the age of 2 weeks. She was normal mentally but retarded physically. Her complaints were general weakness, fatigue, and exertional dyspnea. These symptoms had progressed rapidly during the preceding 3 or 4 months.

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On physical examination the patient was underdeveloped and undernourished. Blood pressure was 110/40. There were no symptoms of peripheral venous congestion and she was not cyanotic. A grade 2-3 systolic thrill was palpated over the left precordium. The pulmonary second sound was moderately accentuated and split. A grade 3 harsh systolic murmur was heard over the whole left precordium and sternum with radiation to the pulmonary artery. In the second and third intercostal spaces at the right border of the sternum, a different systolic-diastolic murmur was auscultated.

Roentgenograms and fluoroscopy of the chest revealed enlargement of the heart, principally in the right ventricle and auricle, but the left ventricle was enlarged also. The pulmonary conus was prominent and pulsated expansively. Increased pulmonary vascular markings were found. Electrocardiography disclosed a left ventricular preponderance, incomplete right bundle branch block, diphasic T waves in the third lead, and negative T waves in the 1-4 chest leads. The phonocardiogram was in accordance with the auscultatory findings.

Heart catheterization studies showed normal pressure tracings in the great systemic veins, right heart, and pulmonary circulation. The oxygen content of the blood samples indicated an increase in O_2 saturation at the lower part of the right atrium, suggesting a large left-to-right shunt. Other laboratory data included a hemoglobin of 11.5 Gm. per cent, red blood cell count 4.2 million, and white blood cell count 11,700. Urinalysis was negative.

Fig. 1.—P. B. Chest x-ray film showing pulmonary vascular engorgement and dilatation of the left ventricle.

An effort was made to evaluate the complex clinical picture of the patient. The results of the hemodynamic examination strongly favored interatrial septal defect; however, certain clinical findings (systolic-diastolic murmur, enlargement of the left ventricle, and widened pulse pressure) were not in accordance with this diagnosis. The catheterization was repeated, but similar conclusions were drawn from the results, namely, left-to-right shunt at the level of the right atrium. A preoperative diagnosis of interatrial septal defect was made and surgical repair was decided upon.

The patient was readmitted to the hospital on March 21, 1958, for surgical correction of the presumed defect. With the patient under endotracheal ether-oxygen anesthesia, an anterior thoracotomy was performed in the left third and right fourth intercostal spaces. The two incisions were connected by cross-section of the sternum. The femoral vessels were exposed and a heart-lung machine was held ready for cardiopulmonary bypass. The opening of the pericardium revealed a greatly dilated, protuberant right coronary artery. This

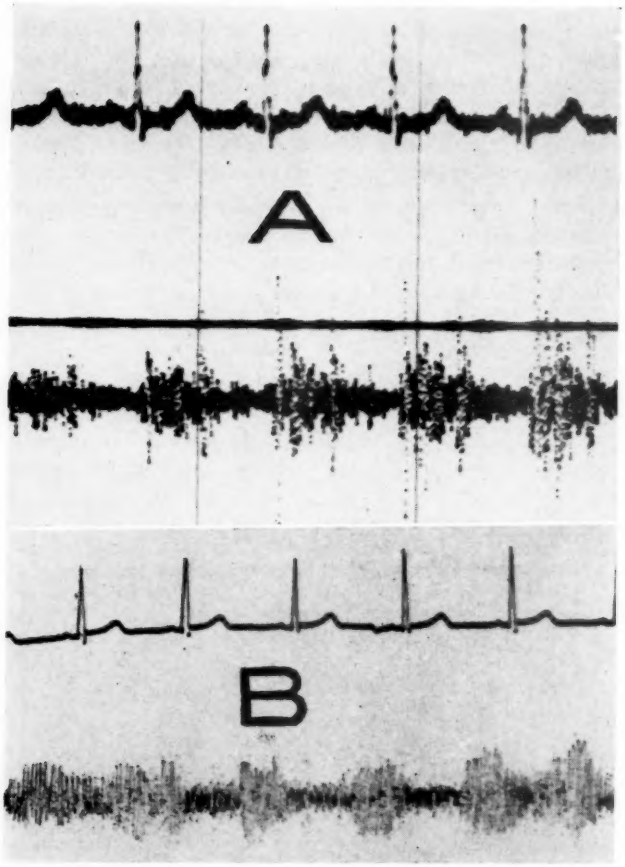

Fig. 2.—Phonocardiogram of patients P. B. (*A*) and H. C. (*B*).

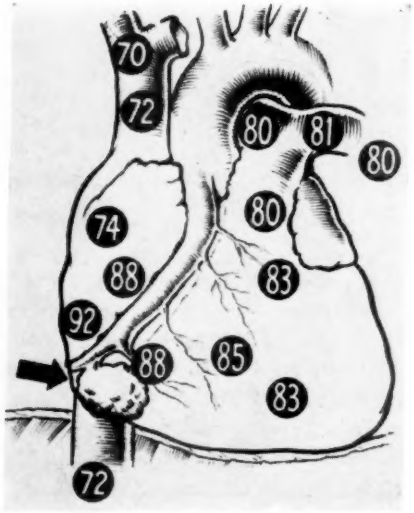

Fig. 3.—P. B. Schematic representation of the results of blood O_2 determinations. The numbers show the O_2 saturation of the blood samples taken by heart catheterization.

vessel originated in the right anterior coronary artery and terminated in an arteriovenous conglomerate close to the terminal part of the coronary sinus. The diameter of the right coronary artery was approximately 7 to 8 mm., and a strong systolic-diastolic thrill was felt over it. The artery was dissected free, and an occluding bulldog clamp was placed around it just proximal to the conglomerate. The occlusion of the vessel caused complete disappearance of the thrill, diminution of the size of the heart, and slowing of the heartbeat. After 5 minutes of occlusion no undesirable effect was observed. The clamp was removed and replaced with two ligatures of 2-0 silk. The edges of the pericardium were approximated loosely. Routine closure of the chest followed, with bilateral drainage of the pleural cavity. The postoperative course of the patient was complicated only by moderate bronchitis. The electrocardiogram performed immediately after the ligature showed inversion of the T waves in the first and second leads and elevated ST segment in the third lead. These changes disappeared within the next 3 days. The patient was discharged in good condition 2 weeks after surgery.

She was followed closely thereafter. Her condition improved rapidly; fatigue and exertional dyspnea disappeared. On x-ray examination, the size of the heart and the pulmonary congestion decreased significantly.

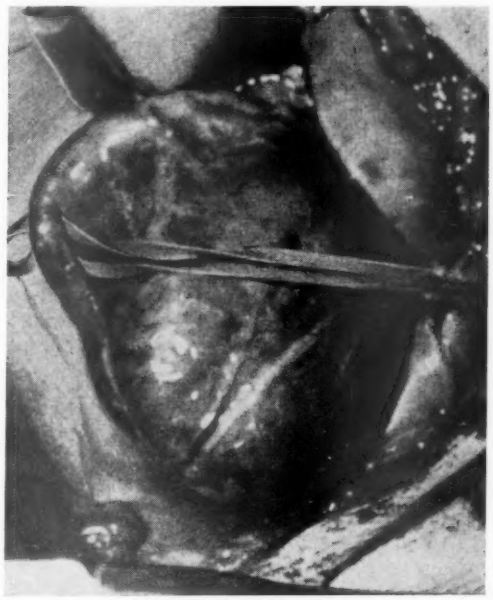

Fig. 4.—P. B. Operative situs. The enormously dilated right coronary artery is well visualized.

CASE 2.—An 18-year-old Negro girl entered the hospital on June 9, 1958, for cardiovascular studies. She was known to have had a cardiac murmur since the age of 7 years. She showed normal mental and physical development, attended school, and took part in housework. The patient stated that for 3 weeks she had felt weak and had noticed night and afternoon sweats with palpitation. There was a history of an orthopedic ankle operation 4 years ago. Otherwise the medical history was essentially negative.

Physical examination revealed a well-developed, well-nourished, alert, Negro girl in no active distress. Blood pressure was 120/65. There were no signs of peripheral venous congestion or cyanosis. The heart was slightly enlarged to the left. Pulse rate was 90 per minute. A very strong, continuous systolic-diastolic thrill was felt in the left third and fourth intercostal spaces parasternally. A grade 4 continuous machinery murmur was auscultated with the same localization and no typical radiation. The intensity of the murmur decreased significantly on compression of the fourth intercostal musculature. The pulmonary second sound was moderately accentuated.

X-rays and fluoroscopy demonstrated slight enlargement of the left ventricle. Electrocardiography disclosed moderate left ventricular preponderance. Phonocardiography showed a typical continuous systolic-diastolic "patent-duct" murmur.

Heart catheterization studies revealed normal pressure relations in the right heart and pulmonary artery. The blood sample taken from the outflow tract of the right ventricle showed relative increase in oxygen content. The sample taken from the coronary sinus disclosed no increase in oxygen saturation. Other laboratory findings were hemoglobin 11.0 Gm. per cent, red blood cell count 3.9 million, and white blood cell count 5,700. Urinalysis was negative.

The machinery character of the systolic-diastolic murmur was strongly indicative of an arteriovenous communication. The localization of this murmur alone excluded a patent duct and the absence of cyanosis, clubbing, and polycythemia was against this being a pulmonary arteriovenous fistula. The elevation of the oxygen content in the right ventricular outflow tract strongly suggested that the communication was between a systemic (coronary) artery and the chamber of the right ventricle. We have to confess that our previous case, operated upon 2 months before, inspired us considerably.

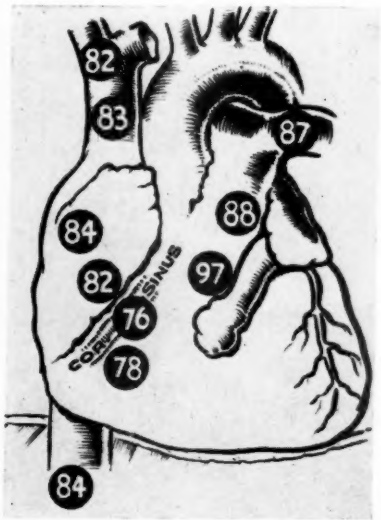

Fig. 5.—H. C. Schematic representation of the results of blood O_2 determinations. The numbers show the O_2 saturation of the blood samples taken by heart catheterization.

The murmur was so strong and the thrill so superficial that we felt ourselves somewhat uncertain regarding the diagnosis; therefore arteriography was performed through the prepared left mammary artery to exclude the possibility of an arteriovenous fistula of the thoracic wall. The result of this examination was essentially negative.

On June 11, 1958, a left anterolateral thoracotomy was performed with a preoperative diagnosis of an anomalous connection between one of the coronary arteries and the outflow tract of the right ventricle. With the patient under endotracheal ether-oxygen anesthesia, the left pleural cavity was entered through the fourth intercostal space. After opening the pericardium we found the left coronary artery extremely dilated (approximately 8 to 9 mm.), tortuous, and ending in a paper-thin wall aneurysm which communicated directly with the right ventricle. This abnormal vessel was dissected free and occluded temporarily by a bulldog clamp. After waiting 5 minutes, the clamp was replaced by two 2-0 silk ligatures and the vessel and the aneurysm were occluded. Routine closure of the chest followed with drainage of the pleural cavity. The pericardium was left open.

The patient tolerated the procedure well and had an uneventful postoperative course. The electrocardiogram showed transient inversion of T waves in Leads I, II, and III during the first postoperative week. She was discharged from the hospital 12 days after surgery.

TABLE I. RESULTS OF THE HEMODYNAMIC EXAMINATIONS

PATIENT (AGE)	PRESSURE (MM. HG)			OXYGEN CONTENT (VOLUME PER CENT)								FLOW (L./MIN.)		
	SYSTEMIC	PULMONARY ARTERY	PULMONARY WEDGE	CORONARY SINUS	SUPERIOR VENA CAVA	INFERIOR VENA CAVA	RIGHT ATRIUM	RIGHT VENTRICLE	PULMONARY ARTERY	FEMORAL ARTERY	CAPACITY	SYSTEMIC	PULMONARY	SHUNT
P. B. 4 yr.	110/40	28/15	14/10	—	9.8 10.1	10.1	10.2 12.3 12.9	12.3 11.9 11.6 11.6 11.2	11.2 11.4 11.2	13.9	14.0	2.05	3.41	1.36
H. C. 18 yr.	120/65	22/8	14/8	12.4	13.3 13.4	13.5	13.3 13.5	13.0 15.9	14.4 14.3	16.2	16.4	5.62	6.78	1.16

A. *B.*

Fig. 6.—H. C. Operative situs before (*A*) and after (*B*) the ligation of the anomalous coronary artery. The arteriovenous aneurysm is well visualized.

DISCUSSION

The few articles written on anomalous coronary arterial drainage all agree that the clinical diagnosis of this disease is extremely improbable. Some of the authors express the thought that this anomaly can be diagnosed only at autopsy. It is our opinion that the symptoms and hemodynamic findings of this disease are so characteristic that the diagnosis should be made as in any other common congenital abnormalities of the heart if one considers the possibility of this rare condition.

The clinical picture in anomalous coronary arterial drainage is that of a systemic arteriovenous fistula with an intracardiac shunt. These signs may be or may not be accompanied by symptoms of myocardial insufficiency.

Arterial blood draining in large quantities through the fistula and directly into the coronary sinus or into the right heart increases enormously the coronary blood flow but at the same time may decrease significantly the quantity of blood flowing through the myocardial capillary bed. The heart presents a typical picture of a left-to-right shunt (that is, increased pulmonary vascular markings, dilatation of the right ventricle, and so forth). On the other hand, the widened pulse pressure, enlargement of the left ventricle, deviation of the main electrical axis to the left, and the continuous systolic-diastolic murmur are characteristic findings of an arteriovenous fistula. This unusual combination of clinical symptoms is very typical of a coronary arteriovenous fistula.

In the differentiation from the other anomalies causing similar symptoms (arteriovenous fistula of the thoracic wall or mediastinum and so forth), right heart catheterization may give considerable support. Before establishing an operative indication for congenital heart disease, we perform heart catheterization routinely, even in so-called "typical" cases. Probably this seems unnecessary in some cases but it has produced no untoward effects and we have saved ourselves from several surprises at the time of operation.

By demonstrating a relative increase in the oxygen content of the blood in the coronary sinus, right atrium, or ventricle, we may support a diagnosis of the anomalous drainage.

Regarding the therapy of the coronary arteriovenous fistula, opinions differ considerably. Some authors[21] describe the disease as a benign anomaly which has no serious, if any, clinical consequences; others report patients that died in heart failure caused by the fistula.[10] It is our opinion that the management of the coronary arteriovenous fistula does not differ from the therapy of other systemic arteriovenous communications, namely, surgical interruption of the connection. The unusual localization and the special hemodynamic features do not contraindicate surgery but make it urgent. The opposition based upon fear of ligating a coronary artery is not tenable, because the disease represents a *circulus vitiosus;* on one hand the increased recirculating blood volume places a considerable burden on the myocardium, and on the other hand the fistula directly impairs the myocardial blood supply by "sucking out" the blood from the coronary system. In this way the ligature of the afferent vessel does not impair the myocardial blood supply but influences it favorably.

The operative technique must be simple. It is our feeling that the radical dissection and extirpation of the arteriovenous conglomerate or fistula is unnecessary and hazardous, and multiple ligation of the afferent artery is sufficient. The ligatures should be placed as close to the communication as possible to preserve the proximal tributaries of the coronary artery. It is advisable to occlude the vessel temporarily before applying the definitive ligature. The occurrence of a large infarct or severe arrhythmias indicates that the site of the ligation was not properly placed and consequently must be changed.

SUMMARY

Two cases of abnormal coronary arterial drainage successfully operated upon are presented. The clinical picture of this unusual disease is described

and the opinion is expressed that all coronary arteriovenous fistulas may be diagnosed clinically and treated surgically.

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Editorials

CONDUCTED BY I. S. RAVDIN, M.D.

The Diagnosis and Management of Bleeding From the "Lower" Intestine

Bleeding from the gastrointestinal tract is often a serious and confusing occurrence. When blood appears in the vomitus or aspirated gastric contents, the bleeding lesion can almost always be located proximal to the ligament of Treitz. This may suggest several diagnostic possibilities, but at least the site of bleeding can be localized to a relatively small area of the gastrointestinal tract.

When melena occurs or actual blood and clots are passed per rectum, there is no method of localizing the site of the bleeding. The color and appearance of the rectal discharges are in some cases indicative of a bleeding point higher or lower in the intestinal tract, thus black "tarry" stools may indicate hemorrhage from a lesion high in the intestinal tract, whereas the passage of cherry-colored clots might be thought to have come from a bleeding source in the lower colon. Although this line of reasoning is often correct, it is also true that the speed and amount of bleeding and the speed of intestinal transport are factors that may alter the appearance of blood discharged per rectum. At times a patient with a rapidly bleeding duodenal ulcer may pass blood and clots per rectum.

Bleeding that occurs proximal to the ligament of Treitz can usually be diagnosed clinically with the help of appropriate studies. Bleeding that comes from sites below the ligament of Treitz is more difficult and at times impossible to localize or diagnose. X-ray studies of the small bowel and colon and sigmoidoscopic examination usually permit a diagnosis of the more common lesions that bleed such as carcinomas and some other tumors, ulcerative colitis, diverticulitis, and polyps. But in spite of exhaustive studies, many patients show evidence of chronic blood loss from the gastrointestinal tract or even of massive bleeding without any diagnostic finding to indicate the source of the bleeding. When such bleedings are repeated or when massive hemorrhage does not cease after adequate blood replacement, I believe that laparotomy should be looked upon as a diagnostic as well as a lifesaving therapeutic procedure. It is an advantage if the laparotomy can be performed while the bleeding is taking place. This helps to localize the bleeding site, especially if the bleeding lesion is in the small intestine. Experience has shown that the upper limit of blood in the small intestine is within 12 inches of the bleeding point. If operation is delayed until the bleeding stops, this valuable marker is lost because the intestinal flow rapidly cleanses the intestinal lumen of blood. If bleeding is from the wall of the colon, blood is not

found in the lumen of the gut proximal to the ileocecal valve. These are practical aids when a search is made for a bleeding lesion undiagnosed preoperatively.

At operation the bleeding lesion is often easily discovered and treated. In the small intestine we have found such undiagnosed lesions as peptic ulcerations of Meckel's diverticulum, stress ulcers, leiomyomas, neurofibromas, and other tumors and non-Meckelean diverticula. Resection of the lesion resulted in a cure.

There is a group of cases, however, in which a thorough search fails to disclose any bleeding lesion on external examination of the small intestine and colon or by palpation. These are the cases in which the surgeon is faced with a most difficult problem of diagnosis and choice of treatment.

Unless the patient is operated upon while the bleeding is going on, there is no way to localize the bleeding site. If the patient is actively bleeding at the time of operation, as shown by blood in the small intestine, the upper limit of the blood in the gut is identified by aspiration with a needle and glass syringe. The bleeding area should be approximately 12 inches above or below this point. If careful inspection of the intestine fails to show any lesion to account for the bleeding, the gut is opened and intussuscepted cephalad and caudad. In this way the mucosa may be inspected for a distance of 6 or 8 inches. Occasionally tiny telangiectatic areas may be found as the cause of bleeding. If no bleeding areas are found, approximately 2 feet of intestine are resected including the stoma through which the gut was explored. Experience with such "blind" resections in several cases of acute bleeding, and in others previously unsuccessfully explored when the bleeding had stopped, has led to the discovery of minute bleeding points (telangiectasis?) in 3 cases, acute ulcer in 2 cases, and nothing to explain the bleeding in 2 cases. In none of the cases treated by "blind" resection at the upper limit of blood in the intestine has there been a recurrence of melena. One of the patients in whom no bleeding lesion was found had had numerous admissions for rectal hemorrhage and two previous negative explorations. She has not bled in the 3 years following the intestinal resection.

In cases in which no blood is found above the ileocecal valve, and with the bowel full of dark bloody contents, the localization of the bleeding point in the colon is extremely difficult if not impossible. Most of these patients are in the older age group and are hypertensive with marked sclerotic changes as evidenced by aortic and iliac enlargement. Many of them have diverticulosis of the colon, most marked in the sigmoid but in many cases present throughout the colon. The indication for operation has been massive recurring or exsanguinating hemorrhage from the bowel, a complication to which these patients react poorly. The operation should not present a more traumatic situation because of its extent or duration. Therefore, some plan of action should be formulated which should avoid delay and confine the operation to the area of bleeding if possible.

A rapid inspection of the colon will often suggest that the blood appears fresher on the right or left side. Careful inspection of the colon may lead to the discovery of a small area of subserosal dilated vessels, mostly veins. A

colotomy in this area has led to the discovery of a hemorrhaging telangiectatic site in the right colon in 4 cases. A conservative right colectomy including the telangiectasis has resulted in a cessation of bleeding in all cases.

When it is not possible to determine where the blood in the colon is the freshest, multiple small colotomies may be performed beginning at the site where the blood seems most fresh by external observation. The contents of the colon are inspected. A second colotomy 8 inches caudad or cephalad may show fresher blood or clots or less blood and more normal fecal material. If the blood in the lumen appears to be more recently shed, the inference is that an approach is being made toward the bleeding point. (Endoscopic examination of the bowel lumen through colotomies in cases of bleeding from the colon of undetermined origin has proved useless, time consuming, and an added factor of contamination.) One of two alternatives is now open to the surgeon. He may perform a "blind" resection of the area of the colon which appears to be the area from which the bleeding is taking place. This seems logical if the area contains many diverticula because of the known association of bleeding and diverticulosis. When the diverticulosis is mostly of the sigmoid, a left colectomy is carried out. In one case in our experience where the entire bowel was filled with blood and there was a generalized diverticulosis, a total colectomy and anastomosis of the ileum to the sigmoid at the sacral promontory was performed. Bleeding stopped in these cases and there was no operative mortality. In none of the 3 cases of exsanguinating hemorrhage associated with diverticula, treated by colon resection, was a bleeding site found on pathologic examination of the specimen.

The second alternative open to the surgeon when there is no indication of the bleeding site can be used if the hemorrhage is less massive and the operation less of an emergency. A temporary transverse colostomy may be performed. If blood then appears at the proximal colostomy stoma, the bleeding site in the right colon can be treated by right colonic resection; if blood continues to appear per rectum, the bleeding area must be in the left colon or sigmoid and a left colectomy may be performed. In these cases, the area from which the bleeding comes is resected because it is impossible to discover the bleeding point.

These are not easy solutions to the determination of the bleeding site in the colon, but I have found no easy solution to this problem, which in many cases even confuses the pathologist.

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One Oft-Neglected Factor Related to Wound Healing

Abdominal wound dehiscence is a statistically common postoperative surgical complication. Surgical literature excuses this by pointing out that urgent surgery cannot always be postponed in the aged and debilitated and

that nutritional deficiencies cannot be corrected overnight. Surgical literature is replete with tomes concerning nutrition and wound healing. I would like to propose that postoperative wound dehiscence and evisceration should usually be accepted as an example of correctable technical failure. Some would have you believe that if the patient is in good condition, the wound will close itself. The truth of the matter is that dehiscence is rare if more attention is given to choice of incision and careful closure of the abdominal wall.

Early in my surgical career, I repaired many incisional hernias. Twenty years or more ago, before this day of good anesthesia, there was some excuse for large incisions rapidly accomplished and rapidly repaired. Today there is none. The plan of the incision and its closure should be included as an integral part of the operative plan. The tournament golf professional who plays beautifully from tee to green will starve to death if he neglects to perfect his putting touch. The surgeon who neglects the wound makes his patient pay a useless price in complications which may be expensive and painful and can be fatal.

It would seem proper for one who suffers the dehiscence hex to examine his own technique and make some adjustments. I considered such an adjustment necessary over 7 years ago. I had had my share of weak wound complications and not all of them were in the malnourished or vitamin-deficient patients.

My particular method of adjustment was about as follows. Provided adequate exposure can be obtained, and it usually can, the abdominal incision of choice is the transverse or modified transverse approach. This is not only more anatomic as far as muscle and fascial planes are concerned but results in a more cosmetic surface scar. After the intra-abdominal portion of the operation is completed, this anatomic wound is carefully closed with interrupted No. 32 alloy steel wire. Since this method was introduced, weak wound problems disappeared as if by magic. I still grudgingly employ the vertical incision when it seems necessary for purposes of exposure. The dehiscence I had last year was the result of one of these necessary digressions.

It is not the purpose of this brief discussion to underestimate the importance of proper nutritional and vitamin balance and the avoidance of postoperative distention, or to ignore such considerations as the biologic aspects of fibrogenesis and wound healing. Also, no one appreciates better than I the advantages of good exposure. But, don't forget to close the incision!

The well-planned operation should include a plan of the incision and of its successful and permanent closure. The operation is not completed until the incision is closed and convalescence is not satisfactory unless it stays closed.

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Book Review

CONDUCTED BY J. GARROTT ALLEN, M.D.

Dentistry for Children. John C. Brauer, William W. Demeritt, L. B. Higley, Roy L. Lindahl, Maury Massler, and Isaac Schour. New York, 1958, McGraw-Hill Company, Inc. Price $11.00.

This fourth edition of *Dentistry for Children,* written by John C. Brauer and others, is similar to the previous edition. The second half again deals with the technical phase of children's dentistry and contains a wealth of material which can be used both by students and general practitioners of dentistry. It is designed as a text for undergraduate and graduate students in pedodontics, as a reference source of information for general practitioners, and is also a source that many physicians may wish to employ in understanding some of the oral and dental problems associated with children. Because of its definite clinical orientation, this edition fulfills its purpose more with undergraduate students and general practitioners of dentistry than with the graduate student in pedodontics.

The addition of a few new illustrations and slight revision of the material by incorporating recent research advances in dental procedures has made this a modern text. The greatest change appears in the chapters on pulp and root canal therapy and operative dentistry. The chapter dealing with oral surgery, although written by Roy L. Lindahl this time instead of John C. Brauer, shows very little change.

The sections on nutrition and the development, morphology, and histology of the teeth are among the stronger areas in this book. More coverage of the embryology of the head would be of value.

This book presents a good picture of pedodontics in general and is a good base line from which more extensive knowledge can be gained by pursuing certain areas in current research literature.

—Frank J. Orland